PHASE-SELECTIVELY SOLUBLE POLYISOBUTYLENE (PIB)-BOUND CATALYSTS AND THEIR APPLICATIONS IN GREEN SYNTHETIC PROCESSES

A Dissertation

by

YANNAN LIANG

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Chair of Committee,	David E. Bergbreiter
Committee Members,	Daniel A. Singleton
	Karen L. Wooley
	Zhengdong Cheng
Head of Department,	Simon W. North

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ABSTRACT

The use of soluble polymer-supported catalysts in homogeneous catalysis has received heightened attention in the past few decades. Previous studies have shown that PIB oligomers have an excellent phase-selective solubility in nonpolar solvents, this property enables facile catalyst/product separation after reactions. This dissertation describes the study of using PIB as a tool in recovery and reuse of the photoredox catalysts and in the development of novel synthetic methods.

Heptane-soluble PIB-bound Ru(II)-bipyridine complexes [$Ru(PIB\text{-}bpy)_3Cl_2$] were prepared and used as photoredox catalysts in reactions including polymerization, oxidative C-C bond cleavage, and [2 + 2] cycloaddition. The results show that the catalyst can be successfully recovered and reused with leaching levels of ca. 1% of the charged catalyst. In addition, the synthesis of a recyclable PIB-bound 10-phenylphenothiazine (PIB-BTH) organic photoredox catalyst is described. This catalyst can efficiently carry out light-mediated radical polymerizations of methacrylates and can be separated from the polymer product via a simple separation process and reused with no significant loss of catalytic activity.

Cyclopropanation and O-H insertion reactions were carried out using a PIB-bound Rh(II) complex. The results show that the phase-selective solubility of the PIB-bound Rh(II) catalyst in a biphasic heptane/acetonitrile mixture can be used not only to recycle the catalyst but also to suppress the side reactions without the use of conventional slow addition method. These studies also suggest that hydrocarbon

polymer cosolvents can function as antileaching agents that decrease the leaching of a polymer-bound catalyst into the polar phase of a biphasic system. Taking the advantage of PIB's excellent phase-selective solubility, the strategy of carrying out homogeneous catalysis using a continuous-flow reactor has been developed. The PIB-bound transition-metal catalysts can be constantly reused in this process.

DEDICATION

This dissertation is dedicated to my family, especially my mom and dad, for their love and support over the years.

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CHAPTER I

INTRODUCTION

In the past decade, the development of more environmentally benign chemical processes has received heightened attention due to the recognition of the sustainability issues in both academic and industrial fields. This interest in sustainability is also seen in the principles of green chemistry that have been introduced by Anastas and Warner.[1] This concept includes preventing waste production, efficiently utilizing raw materials, using safer chemicals and solvents instead of toxic reagents, utilizing renewable materials, designing energy efficient processes, and applying catalysts in synthesis. In implementing these principles, designing green chemical processes using catalysts is a practical approach. Catalysis has always played a significant role in chemistry. However, in recent years, this role has increased due to the development of highly reactive and selective catalysts for chemical reactions. A number of highly efficient and high selective catalysts have been designed and have been shown to be useful in a wide range of chemical transformations in chemical manufacturing, pharmaceutical industry, and materials synthesis. However, there are several environmental concerns that still exist in using these catalytic processes. These concerns include the high cost of preparation of the catalysts and ligands, toxic metal contamination of the products, and inconvenient separation processes that make catalyst recycling difficult.

The development of solutions for these problems has been extensively studied due to the increasing attention of green chemistry. While much attention has been paid to

the development of new and more efficient catalysts, many of the issues above can be impacted by developing better ways to separate the ligands and catalysts from the products after reactions. If such separations are successful, the ligands and catalysts can be recovered and reused without the loss their catalytic activities. Moreover, more efficient separations can simplify the workup procedures, minimize metal leaching to the product, and reduce the amount of solvent waste.

Green Catalysis Strategies for Organic Synthesis

One strategy for catalyst separation and recovery is to immobilize catalysts on insoluble supports. The method of using insoluble supports in synthesis was introduced by Merrifield[2] and Letsinger[3] in their work on synthesis of peptides and nucleotides using divinylbenzene (DVB) cross-linked polystyrene resin supports. In that work, the insoluble supports immobilized newly synthesized peptides during repetitive amino acid couplings, facilitating an otherwise tedious synthesis with facile workup and purification processes. Other recognized that this process could be applicable to catalysis and that a catalyst on an insoluble support can be separated from the product by simple filtration after the reaction. Since then many different methods of using insoluble materials as supports for ligands and catalysts recovery have been developed.[4-7] The discussion below includes a few select examples like cyclopropanation catalysts on insoluble supports to illustrate this particular approach to catalyst/product separation.

An example of using silica supports would be work by Burguete *et al.* who described using insoluble support immobilized chiral bis(oxazoline) copper (Cu)

complexes as catalysts in cyclopropanation reactions.[8] In this case, the silica-supported bis(oxazoline) ligands were prepared by the reaction of the bis(oxazoline) ligand with the functionalized silica in the presence of azobisisobutyronitrile (AIBN), and then the silica immobilized ligands was allowed to react with $Cu(OTf)_2$ to generate the silica-supported bis(oxazoline) copper complexes **1** and **2** (Figure 1). The catalytic activities of complexes **1** and **2** were examined in the cyclopropanation reaction between styrene and ethyl diazoacetate (Scheme 1). The results indicated that the silica-supported catalysts afforded the desired products in modest yields that are comparable to the corresponding low molecular weight catalysts. However, these silica-supported catalysts showed less controlled enantioselectivity (6%-33% enantiomeric excess (ee)) of the cyclopropanation products compared to the results (29%-80% ee) using homogeneous catalysts.

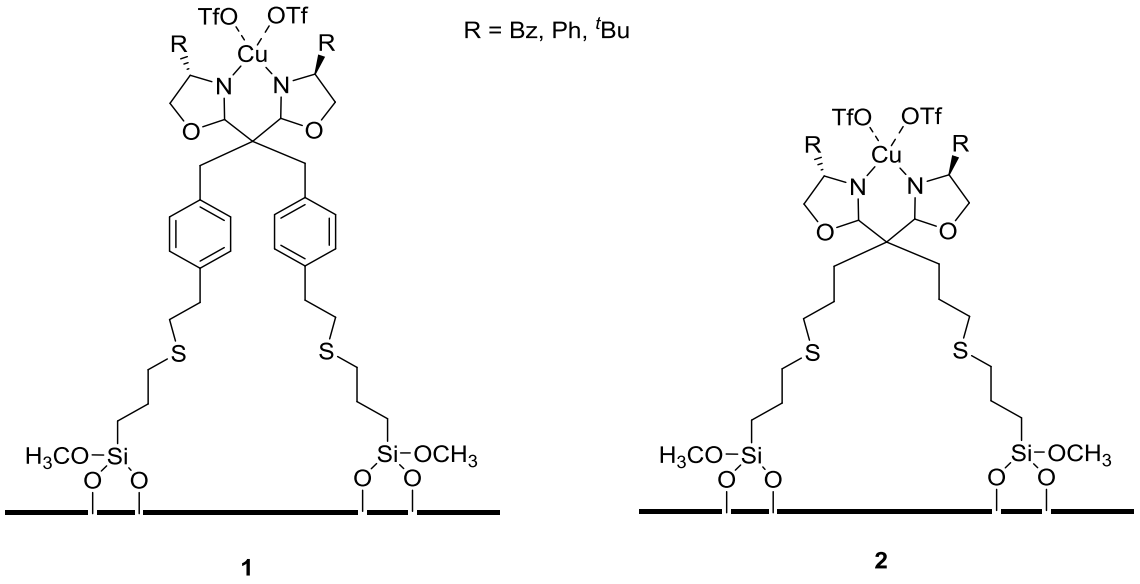
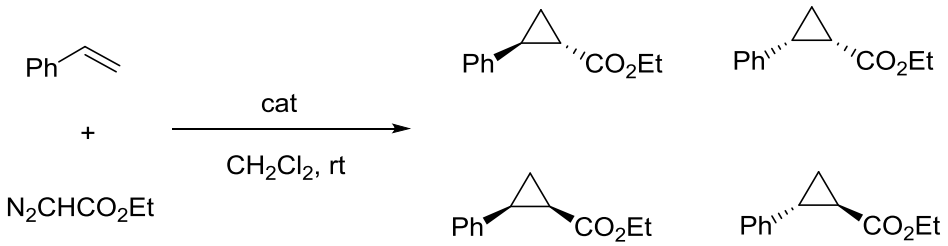


Figure 1. Silica-supported bis(oxazoline) Cu(II) complex.



Scheme 1. Insoluble supports-immobilized Cu complexes catalyzed cyclopropanation reactions of styrene.

In addition, this group used insoluble polymer supports in another approach to immobilize these bis(oxazoline) ligands (Figure 2). The $Cu(OTf)_2$ complexes of the polymer-immobilized ligands **3-5** were again used in the cyclopropanation reactions and afforded products in modest yields with enhanced enantioselectivity (up to 78% ee). After the reactions, the supported catalysts were isolated by filtration and reused under the same conditions for five cycles with no significant loss of activity.

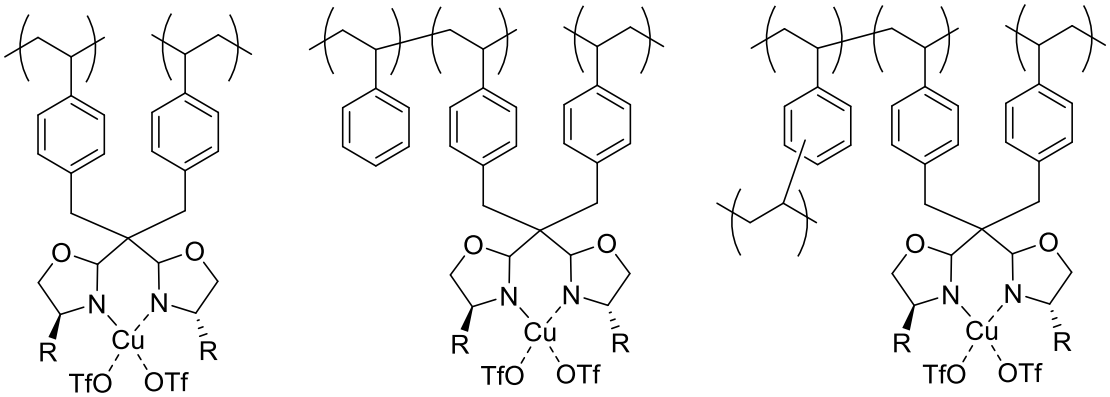
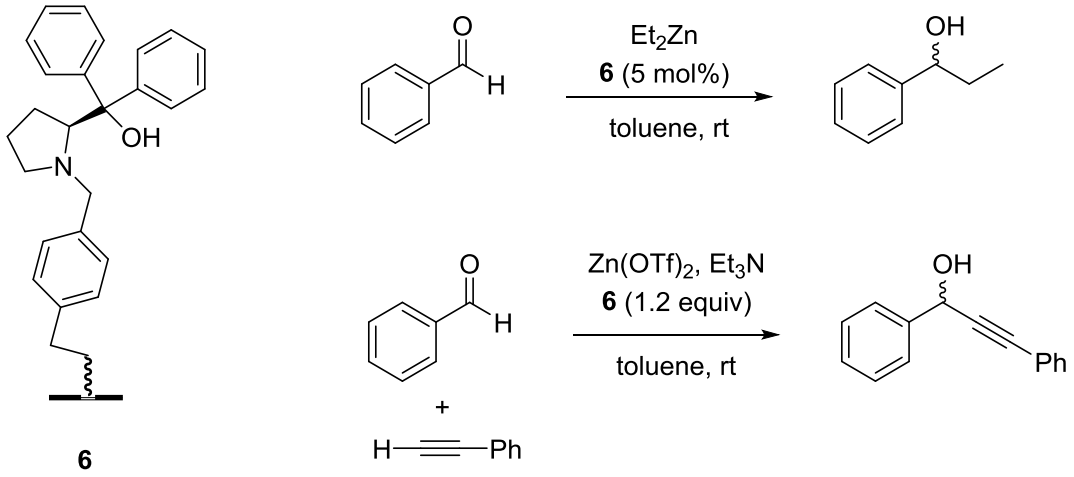


Figure 2. Insoluble polymer-supported bis(oxazoline) Cu(II) complex.

In addition to varying the solubility of a support, the physical form of the support can be varied too. This is illustrated in another example that was reported where Degni and coworkers used fibers instead of resins to support a chiral amino alcohol catalyst useful in asymmetric C–C bond forming reactions.[9] In that work, the *N*-(4-vinylbenzyl)-α,α-diphenyl-L-prolinol ligand was immobilized on polyethylene fibers via an electron



Scheme 2. Insoluble resin-supported chiral amino alcohol catalyzed addition reactions of diethyl zinc or phenylacetylene to benzaldehyde.

beam induced copolymerization technique. The polymer-supported complex **6** was then used in the asymmetric addition of the ethyl groups of diethylzinc to benzaldehyde (Scheme 2). The catalyst **6** afforded the phenylpropanol product in high yield (>95%) but with only moderate enantioselectivity (34%-40% ee). The catalyst recycling was achieved by filtration after the reaction and after which point the fiber-bound prolinol was reused in subsequent cycles. In addition, the complex **6** was also investigated in the

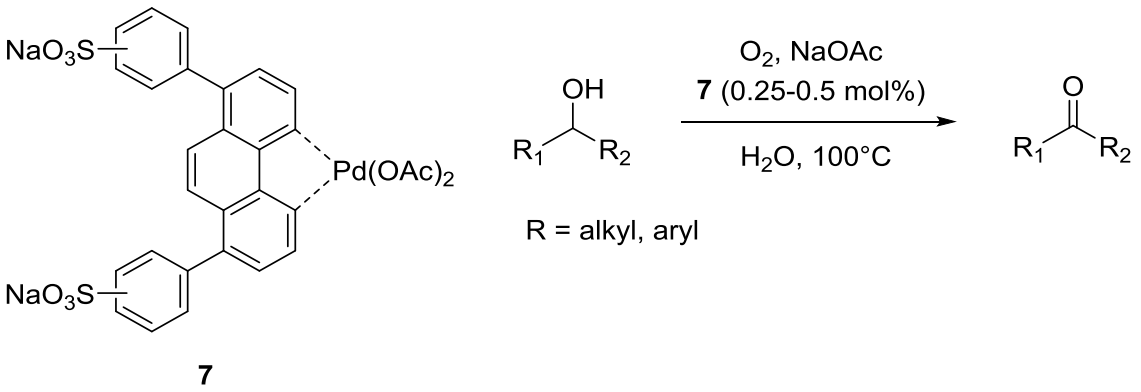
addition of phenylacetylene to benzaldehyde in the presence of triethylamine (Et_3N) and $Zn(OTf)_2$. In this reaction, the corresponding propargylic alcohol was obtained in high ee up to 91%. However, the yields (30%-45%) of the product were modest. The supported catalyst was recovered and reused for two cycles without significant loss of activity.

Although using insoluble supports for catalysts separation and recycling after reactions has the advantage of facile separation of catalysts and products, the heterogeneity of catalysts using the insoluble supports during a reaction leads to problems like modest or different reactivity and less controlled selectivity. In order to address these issues, developing alternative strategies to recover and reuse of catalysts after homogeneous reactions have gained more attention.[10,11] An issue in this approach to recovery of a homogeneous catalyst is that the mutual solubility of the catalyst and product makes catalyst separation from products problematic. Therefore, biphasic separation strategies that involve a separation of the catalyst-containing and the product-containing phase have been developed. Examples of using different biphasic separation techniques for catalysts recycling other than those I have used are discussed below and include aqueous biphasic systems,[12] fluorous biphasic systems,[13,14] and ionic liquid biphasic systems.[15,16]

Water is considered as a green solvent for chemical transformations. Many studies have shown that conducting catalytic reactions in aqueous system using a water-soluble catalyst allows for catalyst and product separation by a liquid/liquid separation method due to the limited solubility of organic compounds in water. A similar strategy

has also been used with surfactant bound catalysts.[17] Using this method catalyst recycling can be achieved under mild conditions.

An example of this approach would be the oxidation of alcohols using a water-soluble palladium (Pd) catalyst that has been described by Sheldon and coworkers.[18] Oxidations of alcohols are often conducted in chlorinated solvents[19] that are not environmentally benign. In Sheldon's work, a water-soluble Pd(II) bathophenanthroline complex **7** was synthesized and used as a recyclable catalyst for the oxidation of alcohols in reactions in water (Scheme 3). The reaction was carried out using catalyst **7**



Scheme 3. Water soluble palladium catalyst catalyzed oxidation of alcohols.

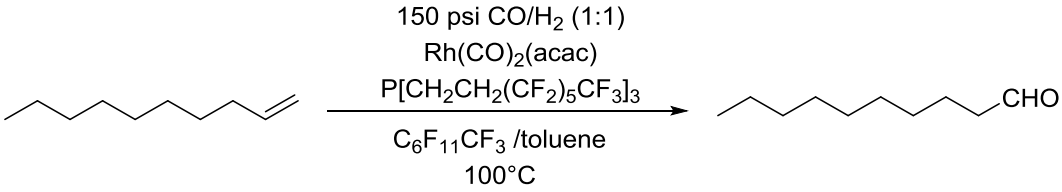
with an alcohol substrate and water in an autoclave. After the reaction was completed, the reaction mixture was cooled to room temperature and depressurized. The product was extracted with diethyl ether from the aqueous phase, and the catalyst-containing aqueous phase was recovered and reused for up to five cycles without a loss of activity or selectivity. A series of alkyl and aryl alcohols were examined and were oxidized to

afford their corresponding aldehydes in satisfactory isolated yields (80-93%) and high selectivity (83-100%). In addition, the author indicated that secondary alcohols that are often less reactive showed high reactivity using this method. For example, 2-pentanol, cyclopentanol, and cyclohexanol had turnover frequency of 100 h^{-1} that is faster than other reported data.

This approach where in the separation of the catalysts in the aqueous phase from a product phase occurs after a reaction has the advantage of easy workup and catalyst isolation. However, it cannot be applied if water-sensitive catalysts or reagents are used. Moreover, the low solubility of organic substrates in aqueous phase sometimes limits its application in a broader range of transformations. An alternative fluorous biphasic system has been developed as an alternative approach to facilitate catalyst separation and recovery. A fluorous biphasic system usually involves a fluorous phase containing the catalyst and another phase that is immiscible with the fluorinated solvent. Using this method, the catalytic reactions can be carried out under either homogeneous thermomorphic conditions or homogeneously in a biphasic mixture of two solvents. The facile separation of the catalyst from the product and reuse the catalyst is then accomplished by gravimetric separation of the fluorous and organic phases.

This idea was first demonstrated by Horvath and coworkers,[20] in chemistry where hydroformylation of olefins was performed in a fluorous system. Hydroformylation reactions are widely used in industry for the synthesis of aldehydes. However, the separation of aldehyde from the catalyst after the reaction can be problematic. In that work, a fluorous phase compatible phosphine ligand

$P[CH_2CH_2(CF_2)_5CF_3]_3$ was prepared via the reaction of 1H,1H,2H-perfluoro-1-octene with PH_3. The hydroformylation of 1-decene was then carried out in a fluorous solvent/toluene system at 100 °C in the presence of CO/H_2 in which the catalyst was generated *in situ* with $Rh(CO)_2(acac)$ and $P[CH_2CH_2(CF_2)_5CF_3]_3$ (Scheme 4). After the reaction, the reaction mixture was cooled to room temperature and depressurized. The fluorous phase was recovered and reused by adding fresh alkene substrate, and the reaction was performed under the same conditions to afford the aldehyde product in a subsequent cycle. These workers showed that only trace amounts of 1-octene were converted to the aldehyde using the recovered organic phase, which indicates that the fluorinated catalyst has good phase-selective solubility and did not leach to the hydrocarbon phase.

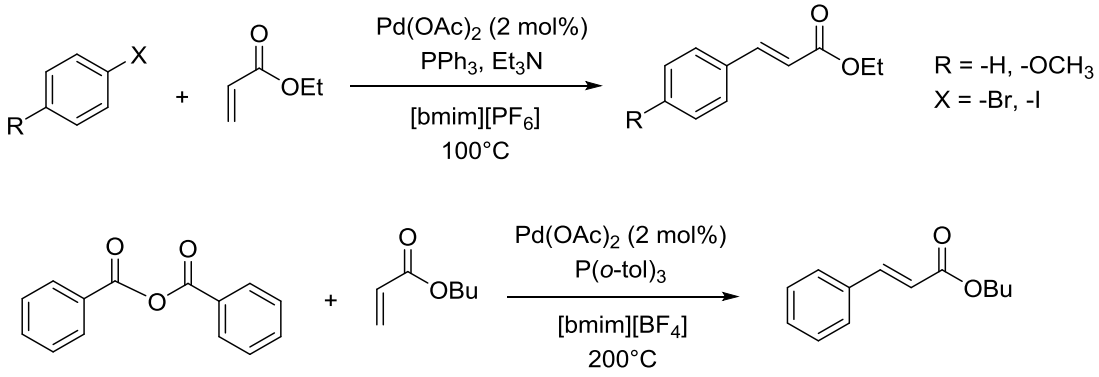


Scheme 4. Hydroformylation of 1-decene under a fluorous system.

Using ionic liquids as solvent media is yet another approach for catalyst/product separation. Ionic liquids have been used as solvents for a variety of chemistry. They are typically insoluble in water and have varying miscibility with organic solvents. By molecularly engineering catalysts such that there is a high solubility of the catalyst in ionic liquids, it is possible to use ionic liquids in a reaction and to then separate the

catalyst-containing ionic liquid phase from the product by biphasic separation. In such a scheme, the catalyst and ionic liquid can be recycled and reused.

Seddon and coworkers have demonstrated this using an example of Pd-catalyzed Heck reactions in ionic liquids.[21] In this case, the coupling reactions of different aryl halides with ethyl acrylate were carried out in an *N*,*N*-dialkylimidazolium or *N*-alkylpyridinium ionic liquid (Scheme 5). The reaction afforded the desired products in



Scheme 5. Pd-catalyzed Heck reactions in ionic liquids.

excellent yields. Moreover, the reaction of a less reactive substrate 4-bromoanisole with ethyl acrylate afforded high yield of the 4-methoxycinnamate. The product was isolated by extraction using cyclohexane, and the catalyst-containing ionic liquid phase was recovered. The recovered catalyst was able to carry out the reaction with fresh substrates through six cycles with no loss of catalytic activity. In addition, the reaction of benzoic anhydride with butyl acrylate was performed using $Pd(OAc)_2$ in the presence of tri-*o*-tolylphosphine in ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate

([bmim][BF_4]). The reaction worked efficiently and afforded the *trans*-butyl cinnamate in 95% yield. The product was isolated by extraction with ether, and the catalyst could be reused with fresh substrate added.

Recovery and Reuse of Soluble Polymer-supported Catalysts

Since most catalytic reactions are carried out in organic solvents, developing strategies for catalyst separation in these systems is of great interest. In recent years, a new concept of using soluble polymers as supports to effect the catalysts recycling has been introduced.[22-25] In this case, catalysts are immobilized on phase selectively soluble polymer supports that can be recovered and reused after homogeneous reactions via facile separation strategies. A number of methods that facilitate the separation of soluble polymer-supported catalysts from products have been described including solid/liquid separations and biphasic liquid/liquid separations.

As shown in Figure 3, there are several approaches to use a solid/liquid separation process to recover a catalyst. For example, a thermomorphic solid/liquid separation system involves the use of a polymer-bound catalyst in a system in which the catalyst is insoluble at ambient temperature but becomes soluble upon heating. This enables the reaction to be carried out under homogeneous conditions most often with some heating. After cooling the reaction mixture, the catalyst is self-separated either as a solid from the product-containing solution. If the polymer-supported catalyst or product separates as a solid the polymer-supported catalyst can be isolated by a simple filtration and reused in the following cycle (Figure 3a and 3b). In a different case, the solid/liquid

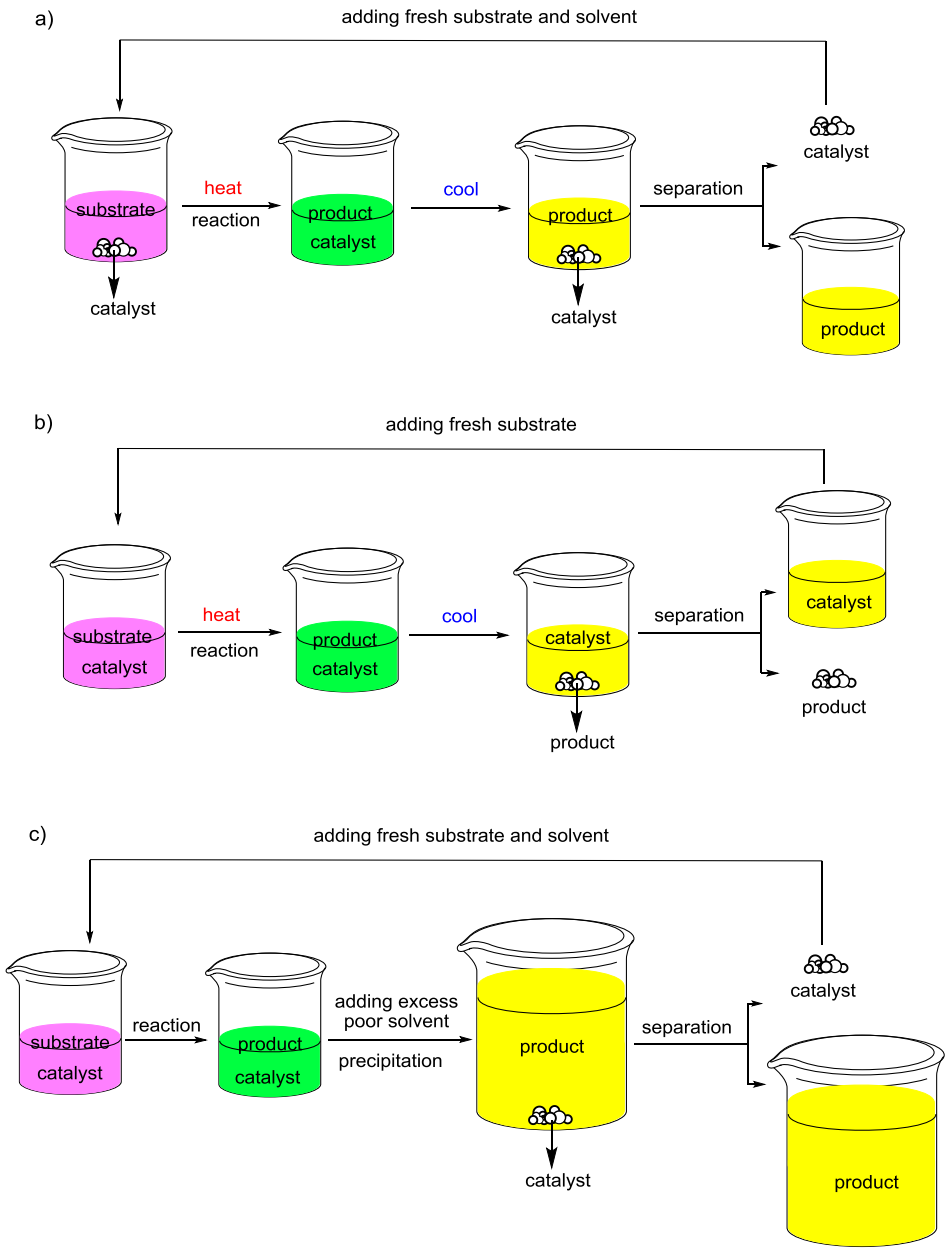


Figure 3. Solid/liquid separation strategies.

separation can be achieved using a phase-selectively soluble polymer-bound catalyst that is dissolved in a homogeneous solution, and the reaction can be conducted at ambient temperature. After the reaction, the polymer-supported catalyst can be precipitated out as

solid by introducing a poor solvent to the homogeneous solution. Then the catalyst can be recovered by a simple filtration and reused in the following cycle while the product stays in the solution (Figure 3c). While both approaches use filtration as the separation technique and while the latter approach is more common, the latter approach as shown has the disadvantage of introducing large amounts of solvent, a possible problem in any large scale application.

An alternative approach is to separate a liquid catalyst-containing phase from a liquid product-containing phase. As shown in Figure 4, this can be accomplished in several ways. In a thermomorphic liquid/liquid biphasic system, a polymer-supported catalyst that is soluble in one phase of a solvent mixture that is immiscible at room temperature is used. In such a system, the solvent mixture becomes homogeneous at elevated temperature. At this point, a catalytic reaction occurs. After the reaction, the reaction mixture is allowed to cool to room temperature leading to reformation of the two phases. If the catalyst and product are in different phases, then a simple gravity separation can isolate the catalyst-containing phase from the product-containing phase. Catalysts can be designed to be in the nonpolar phase if polar products are formed or to dissolve in the polar phase if nonpolar products form (Figure 4a and 4b). A second approach is to use a latent biphasic system (Figure 4c). This sort of scheme involves the use of a polymer-bound catalyst that is soluble in a homogeneous solution of a polar and a nonpolar solvent. The reaction can be conducted at ambient temperature. Perturbation of this monophasic solution by product formation, the addition of salt or the addition of a small volume percent of another solvent

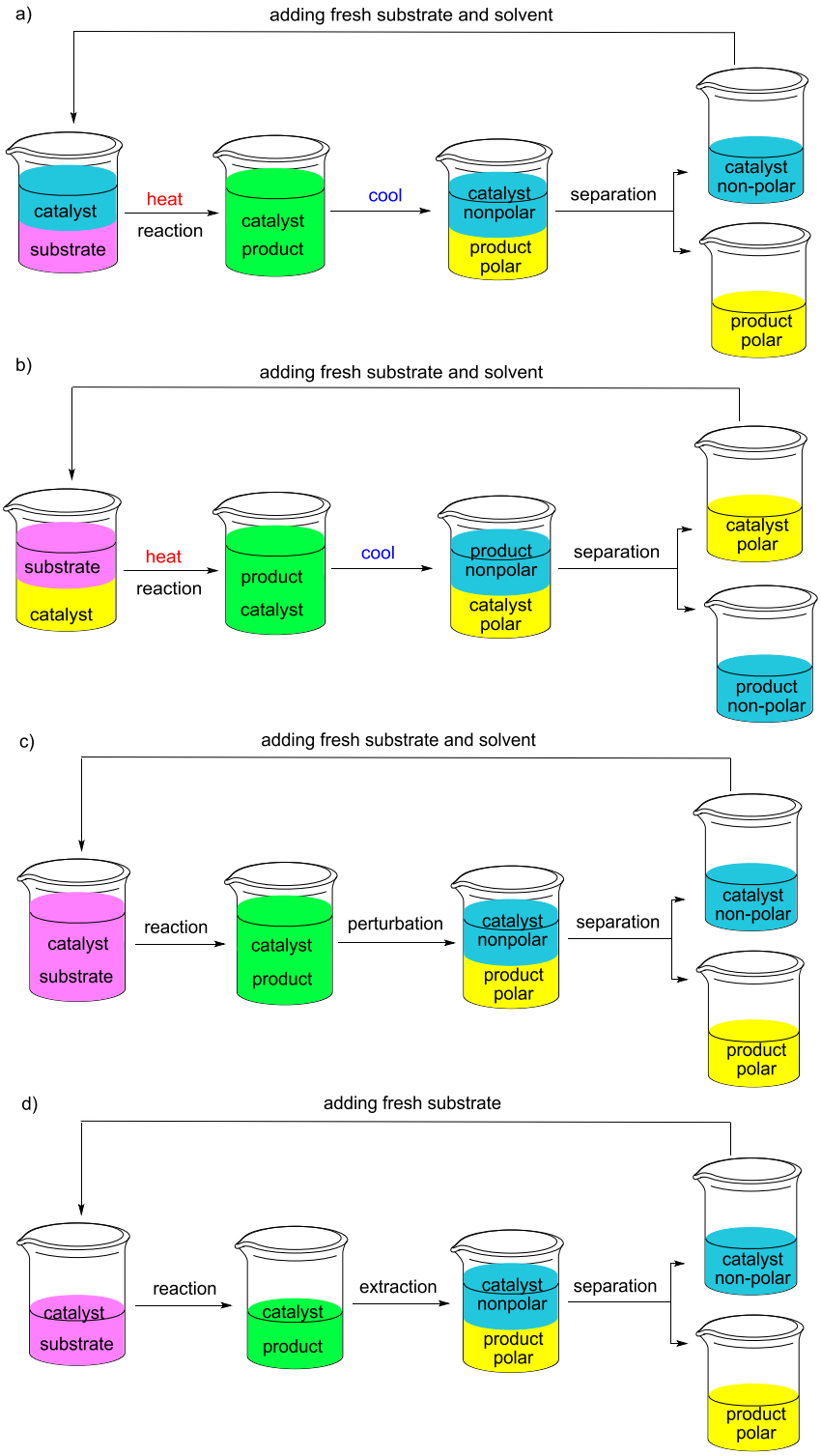


Figure 4. Liquid/liquid separation strategies.

can make this single phase separate into two phases. Then the catalyst-containing phase can be recovered from the product-containing phase. Finally, it is possible to use a more conventional approach too where a soluble polymer-bound catalyst that is soluble in a single solvent system is used to effect a catalytic reaction under homogeneous conditions (Figure 4d). After the reaction, the product can then be isolated by extraction with a solvent that dissolves the product but not the catalyst. In this case, the catalyst-containing phase can be reused in the next cycle with fresh substrates added.

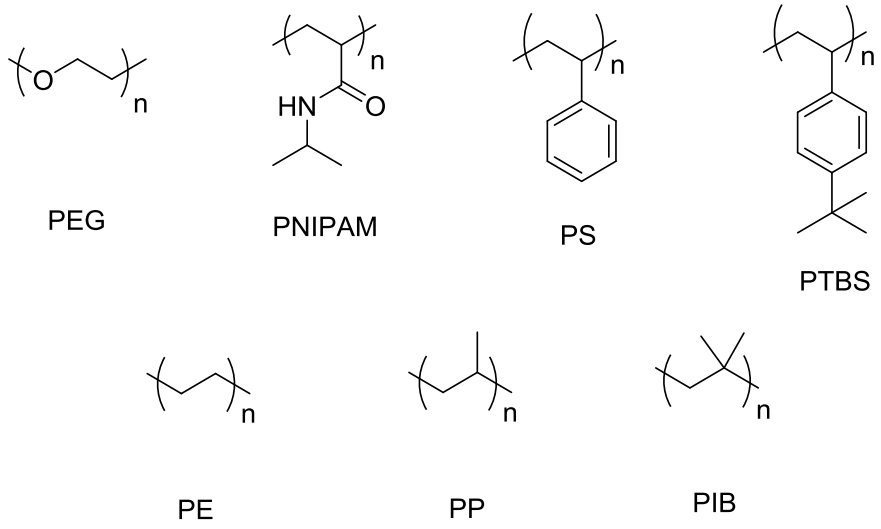


Figure 5. Soluble polymer supports.

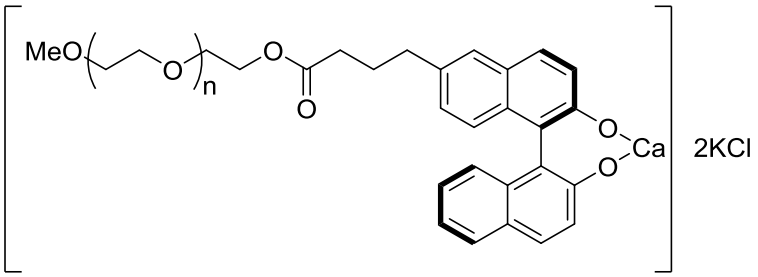
A number of soluble polymers have been developed and applied in catalyst recovery and recycling processes using these separation strategies. As shown in Figure 5, a variety of soluble polymer supports including poly(ethylene glycol) (PEG), poly(*N*-isopropylacrylamide) (PNIPAM), non-cross-linked polystyrene (NCPS), polyethylene

(PE), polypropylene (PP) and polyisobutylene (PIB) have been described. In the following discussion, I have discussed some of the research work the uses these sorts of soluble polymers as supports for catalyst separation and recycling.

Poly(ethylene glycol) (PEG)-Bound Ligands and Catalysts

Poly(ethylene glycol) (PEG) is one of the most widely used soluble polymers for catalyst recovery.[26,27] It is usually synthesized by anionic polymerization of ethylene oxide. PEG is soluble in a wide range of solvents including dichloromethane (DCM), *N*,*N*- dimethylformamide (DMF), acetonitrile (CH_3CN), and water. PEG is insoluble in hexane, heptane, and diethyl ether. This property allows the PEG-supported catalysts to be used in homogeneous reactions and recovered by solvent precipitation and filtration.

An example using PEG is a report by Kumaraswamy and coworkers who have reported the preparation of a PEG-bound BINOL calcium complex and its usage as a recyclable catalyst for asymmetric catalytic reactions.[28] The PEG-bound BINOL complex **8** was examined in the Michael addition reaction (Scheme 6). The reaction was conducted using chalcone and dimethyl malonate in the presence of 15 mol% of **8** under homogeneous system using toluene as the solvent. The results indicated that this reaction afforded the desired product in 90% yield with 32% ee. The complex **8** was also used for the reactions of cyclopentenone and different malonate esters and produced the corresponding products in satisfactory yields (91%-92%) and ee (41%-42%). The catalytic activity of the complex **8** was also investigated in the asymmetric epoxidation of various chalcone substrates using 10 mol% of the catalyst and afforded the epoxide



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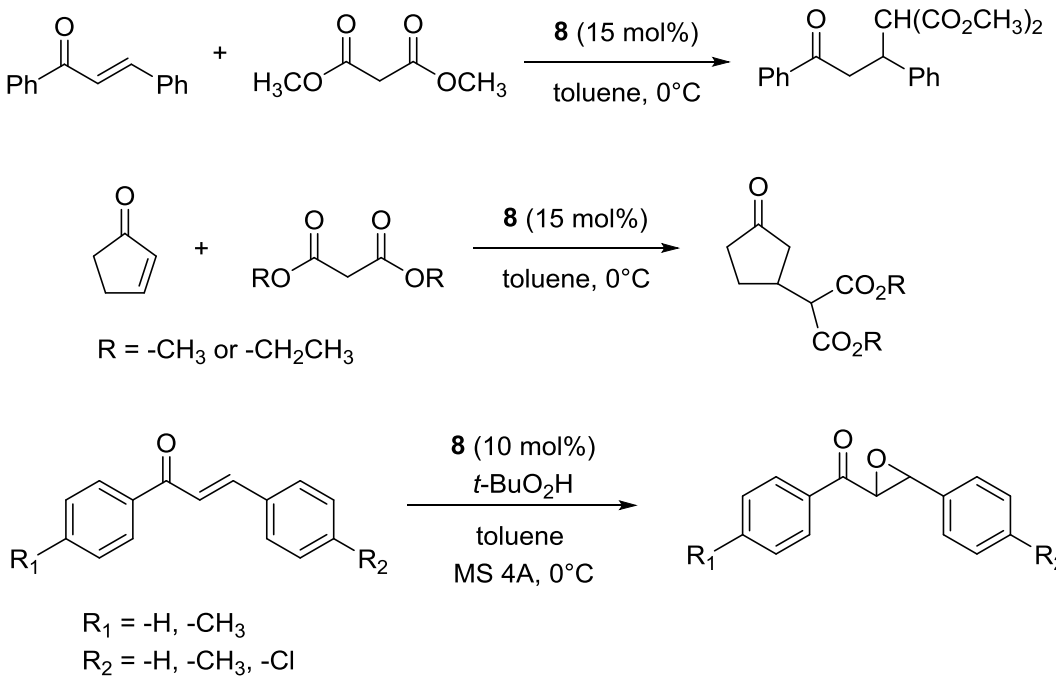
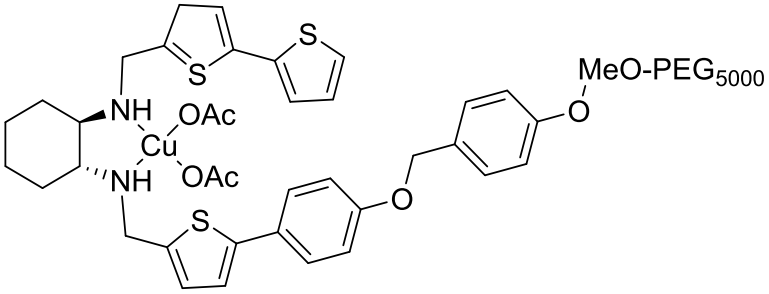


Scheme 6. Michael reactions and epoxidation reactions catalyzed by a recyclable PEG-bound BINOL calcium complex.

products in high yield (>92%) and modest ee (40%-47%). After the reaction was completed, the polymer-supported catalyst was separated from the product by removing the solvent under reduced pressure. The residue was then dissolved in CH_2Cl_2 and

precipitated by adding a large excess diethyl ether. The recovered catalyst was reused up to three cycles and with no significant change in the yield and selectivity.

Bandini and coworkers demonstrated another example of a PEG-support in which a PEG-supported Cu catalyst was used in asymmetric nitroaldol reactions.[29] In that work, a PEG-bound DAT2-Cu(OAc)$_2$ complex **9** was prepared. The complex **9** was



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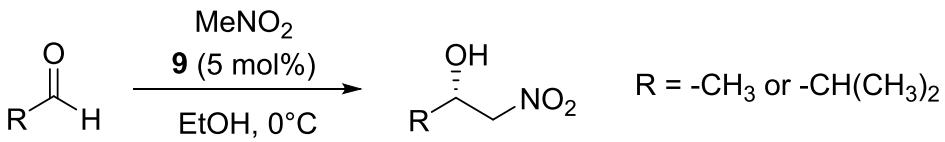
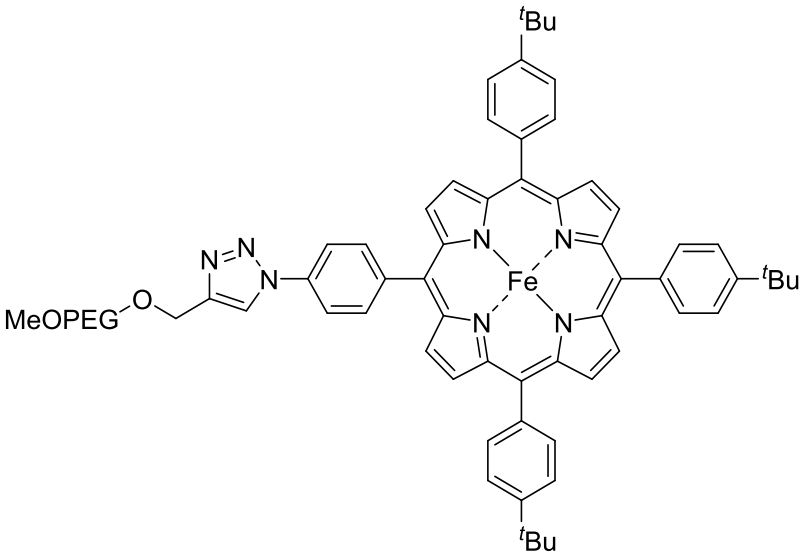


Scheme 7. Henry reactions catalyzed by a recyclable PEG-supported DAT2-Cu(OAc)$_2$ complex.

examined as a recyclable catalyst in Henry reactions of aldehydes and nitromethane (Scheme 7). In this case, the reactions were successfully carried out using 5 mol% of complex **9** in ethanol and generated the desired products in satisfactory yields ranged from 65 to 91% with excellent ee up to 93% under mild conditions. Catalyst recycling was achieved by removing the solvent and washing with diethyl ether, and the recovered

catalyst was used in the subsequent cycle with fresh substrate and solvent added. This PEG-bound catalyst showed good recyclability up to five cycles with no significant loss in activity. In addition, the results indicated that there was no catalyst contamination observed in the crude products.



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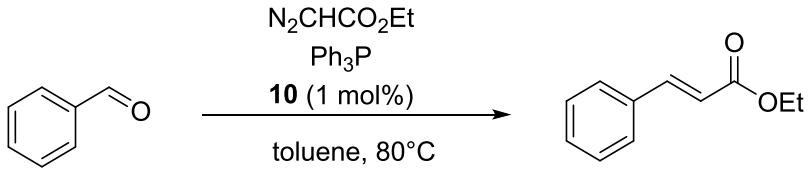


Scheme 8. PEG-bound iron (Fe) porphyrin complex catalyzed olefination of aldehyde.

A third example using a PEG-supported metal complex in homogeneous catalysis was reported by Reiser and coworkers.[30] In the case, the preparation of PEG-bound Fe(II) porphyrin complex **10** was described using a Cu-catalyzed "click"

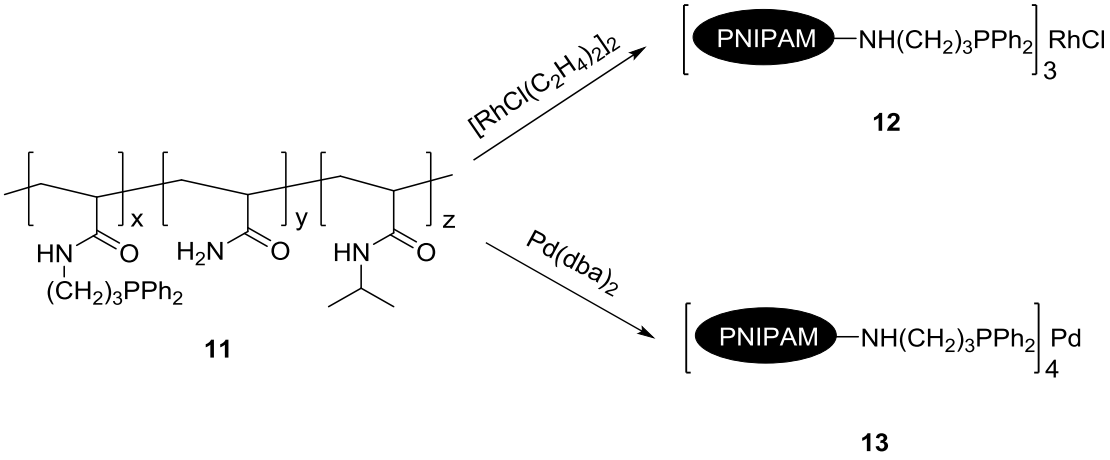
chemistry. To study its catalytic activity and recyclability, olefination of aldehydes with ethyl diazoacetate was performed using 1 mol% of **10** in the presence of triphenylphosphine at 80 °C (Scheme 8). The results showed that complex **10** efficiently catalyzed the reaction and afford the products in excellent yields (73%-99%) with high E/Z regioselectivity. The recyclability of **10** was showed in olefination of benzaldehyde with ethyl diazoacetate. After each run, the complex **10** was recovered by precipitation with excess diethyl ether added and isolated by filtration. The complex **10** was reused for 10 cycles with no significant change in product yield and selectivity.

A disadvantage of all of these PEG based catalysts is that they require a large excess of solvent to precipitate the PEG catalyst for filtration and catalyst recovery. For example, in the case of **8** ca. 1.5 mL of reaction solvent and ca. 120 mL of precipitation solvent would be required to prepare 1 g of product. With **9**, ca. 40 mL of reaction solvent and ca. 60 mL of precipitation solvent would be required to prepare 1 g of product. With **10**, ca. 40 mL of reaction solvent would be required to prepare 1 g of product; however, the amount of precipitation solvent was not mentioned in the report. Thus, while this can be a successful way to separate and recover a catalyst, this approach has a systematic problem in that it uses very large volumes of solvent.

Poly(N-isopropylacrylamide)(PNIPAM)-Bound Ligands and Catalysts

In order to avoid the use of large excess solvent to separate the PEG-supported catalysts in the workup processes, alternative polar soluble polymer supports can be designed. One example is early work by our group that demonstrated the use of

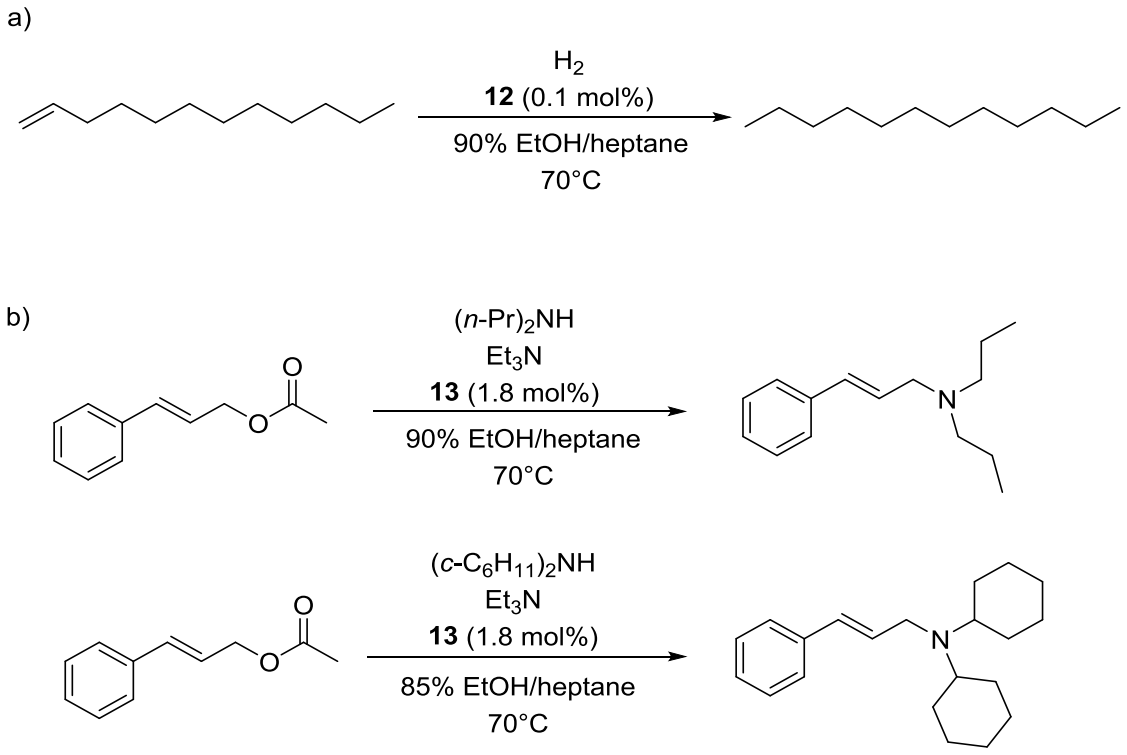
PNIPAM-bound catalysts to effect transition metal catalyzed reactions under homogeneous conditions.[31] In that work, we synthesized a PNIPAM-bound phosphine ligand **11** that was allowed to react with low molecular weight rhodium (Rh) and Pd catalysts to generate the polymer-supported Rh(I) complex **12** and Pd(0) complex **13** (Scheme 9) that were studied as recyclable catalysts in thermomorphic systems.



Scheme 9. Synthesis of PNPAM-supported transition-metal catalysts.

The catalytic activity of PNIPAM-bound Rh(I) complex **12** was investigated in the hydrogenation of 1-dodecene (Scheme 10). The reaction was performed in a 90% EtOH/heptane system at 70 °C. The reaction worked efficiently and formed the dodecane product. After cooling the reaction mixture to room temperature, separation of the product-containing heptane phase from the polar phase that contained the complex **12** occurred. After removing the heptane layer, subsequent reaction cycles were

conducted by adding a heptane solution of fresh 1-dodecene to the EtOH catalyst-containing phase. The polymer- supported catalyst showed excellent recyclability for

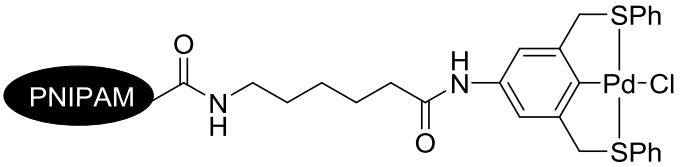


Scheme 10. a) PNIPAM-bound Rh complex catalyzed hydrogenation reaction of 1-dodecene. b) PNIPAM-bound Pd complex catalyzed coupling reactions of amines and cinnamyl acetate.

four cycles without any change in catalyst activity. The phase selective solubility of **12** was studied using the isolated heptane phase to carry out the reaction with 1-dodecene under the same conditions. No reaction occurred. This result also indicates that the PNIPAM-supported catalyst was quantitatively recovered using this method with no Rh

species leaching to the heptane phase. The catalytic activity and recyclability of the polymer-supported Pd(0) catalyst **13** were investigated in the coupling reactions of dicyclohexylamine and dipropylamine to cinnamyl acetate (Scheme 10). The reactions were carried out in aqueous EtOH/heptane solvent mixture at 70 °C. The catalyst was recycled using the strategy described above, and the products were isolated by removing the solvent under reduced pressure to afford the corresponding amines in high purity.

After the success of this chemistry, our group used a similar PNIPAM-bound Pd(0) catalyst for cross coupling reactions under what was described as thermomorphic conditions.[32] In this first example of thermomorphic catalysis, a PNIPAM-bound tridentate SCS-Pd complex **14** was prepared (Scheme 11) and applied in a series of reactions, such as Heck reaction, Sonogashira reaction, and Suzuki reaction. The reactions were carried out in a 90% *N*,*N*-dimethylacetamide (DMA)/heptane thermomorphic system and forming the coupling products from a series of aryl iodides with alkenes, phenylacetylene, and phenylboronic acids in satisfactory yields. The catalyst **14** was recovered using liquid/liquid biphasic separation method and reused for three cycles with no loss in activity.



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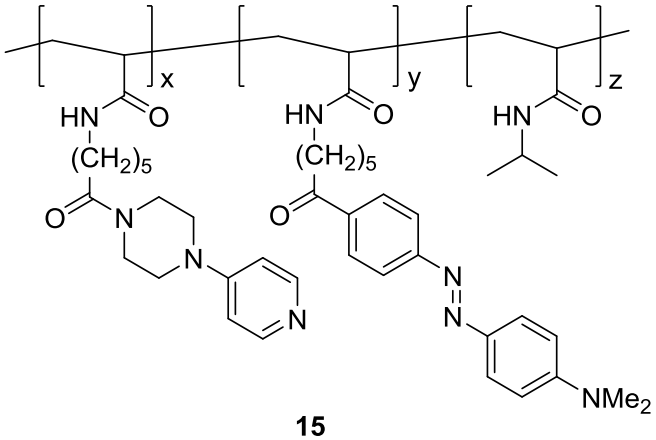
Scheme 11. Recyclable PNIPAM-bound Pd complex.

Shortly after this, we showed an approach of using PNIPAM as a phase-selectively soluble polymer supports for recycling an organocatalyst.[33] In this chemistry, a PNIPAM-bound 4-(dimethylamino)pyridine (DMAP) catalyst **15** was prepared. The UV analysis showed that this polymer-supported complex **15** had an excellent phase selective solubility in the DMF phase (>99.5%) of a DMF/heptane thermomorphic system, which allows the complex **15** to be recovered via liquid/liquid separation after the reaction. Then the complex **15** was examined for the reaction of phenol with di-*tert*-butyl dicarbonate [$(Boc)_2O$] in DMF/heptane solvent mixture at 70 °C (Scheme 12). The results showed that complex **15** can successfully catalyze the reaction to produce the



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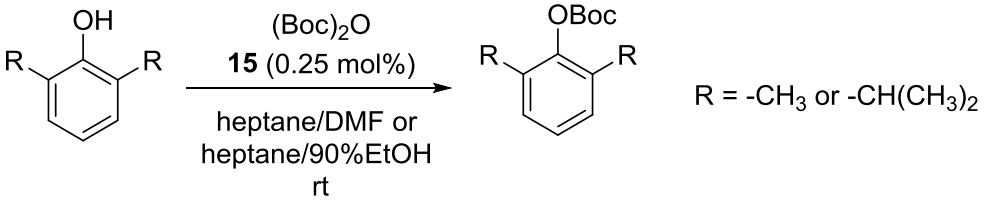


Scheme 12. Acylation reactions catalyzed by a recyclable PNIPAM-bound DMAP catalyst.

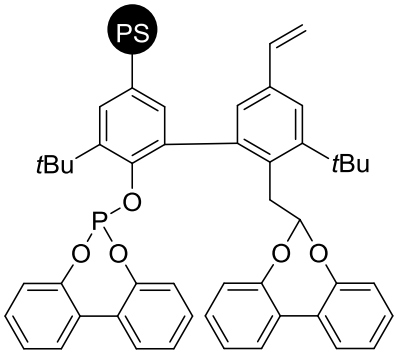
acylation product. After the reaction, two phases were separated after cooling to ambient temperature. The product-containing heptane phase was concentrated under reduced pressure to afford the product. The catalyst-containing DMF phase was then reused with fresh substrate and heptane added. The reactions were also carried out in a 90% EtOH/heptane solvent mixture and gave the products in high yields.

Polystyrene (PS)-Bound Ligands and Catalysts

Polystyrene (PS) is another commonly use soluble polymer support for catalysts recycling.[34,35] It has good solubility in many organic solvents such as toluene, dichloromethane, and THF but is insoluble in water and methanol. In general, PS-supported catalysts can be separated and recovered from the products either by solvent precipitation and filtration or liquid/liquid biphasic separation. There are many examples have described the use of non-cross-linked polystyrene to facilitate the recovery of homogeneous catalysts.

Tunge and coworkers reported the use of a PS-supported biphephos ligand to facilitate Rh-catalyzed reactions.[36] The PS-bound ligand **16** was prepared via a copolymerization reaction with styrene and showed good solubility in THF, dichloromethane, and toluene. The catalytic activity of the phosphine ligand **16** was examined in a 1,4-addition reaction (Scheme 13). The reaction was conducted using a variety of enone and arylboronic acid as the substrates in a toluene solution of $Rh(acac)(CO)_2$ and **16** with a small amount of methanol and water added. The reaction gave high yields (75%-92%) of the hydroarylation products, yields that are comparable

with the low molecular weight catalyst without the use of a large excess of boronic acid. After the reaction was completed, the catalyst was recycled by precipitation via adding an excess amount of methanol to the reaction mixture, and the catalyst was then isolated by filtration and used in subsequent cycles with no significant loss of catalytic activity.



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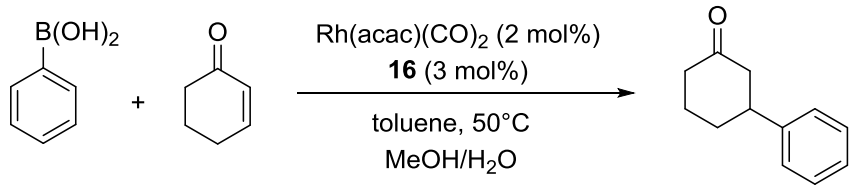
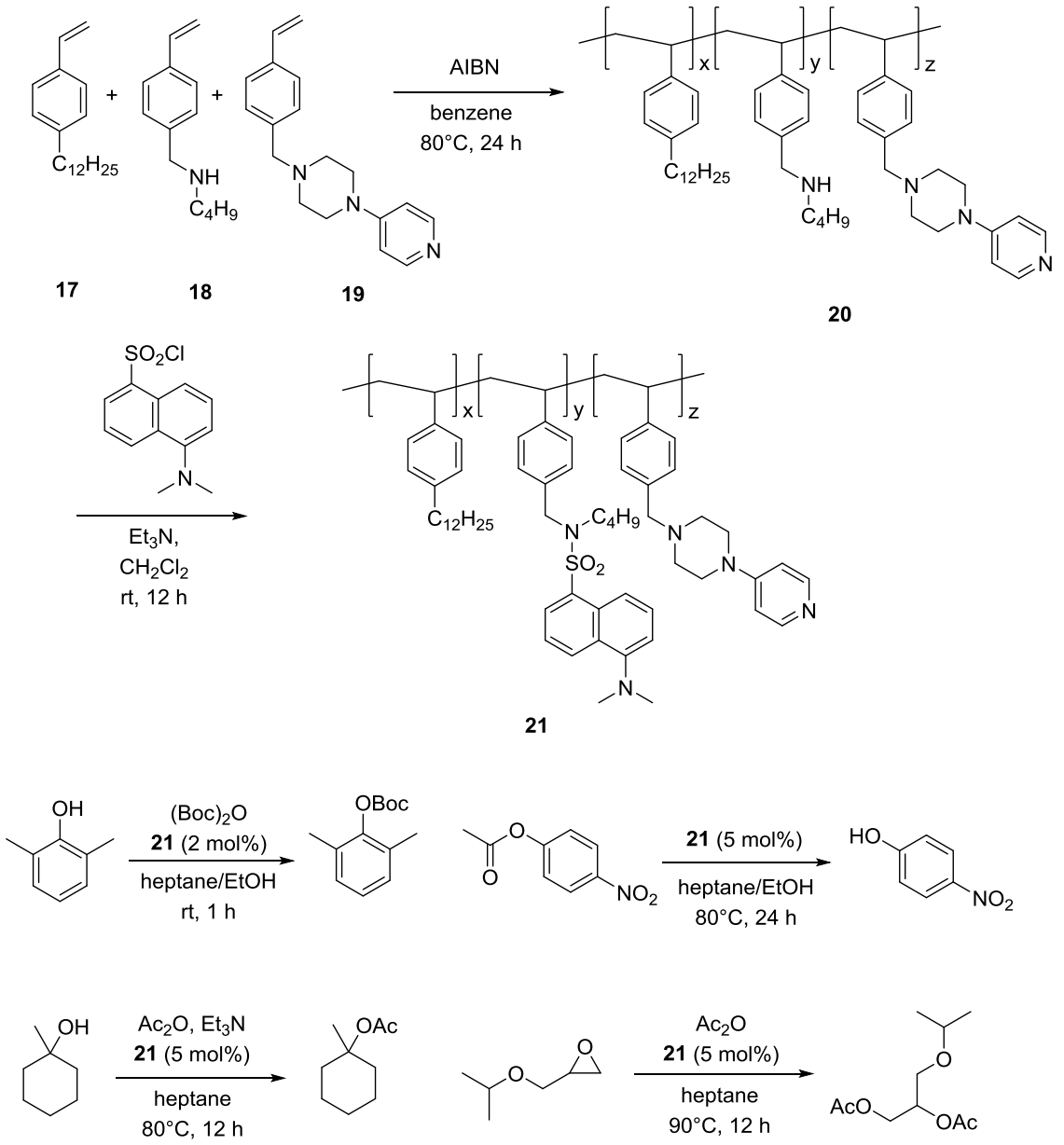


Scheme 13. Polymer-supported biphephos Rh(I) catalyst catalyzed 1,4-addition of boronic acids.

An alternative approach to using polystyrene supports that avoids the need for solvent precipitation is recent work from our group that described the use of poly(4-dodecylstyrene) as a phase-selectively soluble polymer support for recycling of homogeneous organocatalyst using liquid/liquid biphasic separation strategies.[37] The



Scheme 14. Synthesis of a phase-selectively soluble poly(4-dodecylstyrene)-bound DMAP catalyst and it catalyzed reactions under homogeneous conditions.

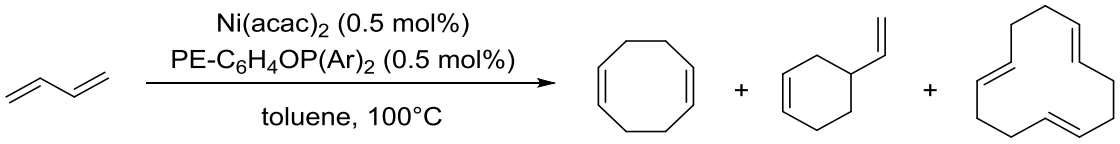
synthesis of the polymer-bound DMAP catalyst was accomplished via copolymerization of 4-dodecylstyrene **17**, (4-vinylbenzyl)butylamine **18** and the DMAP containing

monomer **19** to afford the polymer **20** that was allowed to react with dansyl chloride to form the polymer **21**. This poly(4-dodecylstyrene)-bound DMAP catalyst was then examined in a variety of reactions including formation of Boc esters of phenols, transesterification of 4-nitrophenyl acetate, acylation of alcohols, and acylation of epoxides (Scheme 14). All reactions were carried out under homogeneous conditions. The catalyst recycling was carried out either by addition of water to induce a biphasic liquid/liquid separation or by simple extraction of the reaction mixture to isolate the products with a polar solvent so that the solution of **21** could be recycled. This polymer-supported catalyst was shown to be recovered and reused for up to 20 cycles, and afforded the desired products in excellent isolated yields. The extent of catalyst leaching was analyzed by fluorescence spectroscopy. Only 0.002%-0.09% of **21** leached into the polar phase per cycle.

Polyethylene (PE)-Bound Ligands and Catalysts

Simple hydrocarbon polymers are also useful as non-polar soluble supports. One example is polyethylene (PE) which can be used to prepare a number of recoverable and reusable polymer-bound ligands and catalysts.[38-40] PE oligomers like high molecular weight polyethylene polymers are insoluble in any solvent at ambient temperature and become soluble in solvents like toluene or THF at 80 °C. This property allows the PE-supported ligands and catalysts to catalyze reactions under homogeneous conditions at elevated temperature. The PE oligomer-bound catalyst then forms a precipitate on cooling which can be isolated by filtration at room temperature.

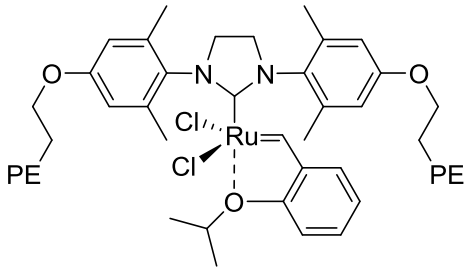
Early work by our group has described the use of PE oligomers as supports for a variety of homogeneous catalysts.[41] In one case, a number of PE-bound alkyl diary1 and triaryl phosphite ligands were synthesized, and these ligands were used to prepare prepared PE-bound nickel (Ni) catalysts. The PE-supported Ni catalysts were used to catalyze cyclooligomerization of butadiene in toluene at 100 °C (Scheme 15). In this homogeneous system, the PE-bound catalysts showed excellent catalytic activity and provided comparable product yield and selectivity as their low molecular weight counterparts. In addition, it was possible to control the product selectivity by varying the ligand/nickel ratio. For example, with the right ligand/catalyst ratio, high selectivity (90%) for formation of 1,5-cyclooctadiene was achieved. Recycling of the catalyst was accomplished using solid/liquid separation strategy after the reaction mixture was cooled to room temperature.



Scheme 15. Ni(0)-catalyzed cyclooligomerization of butadiene using PE-bound phosphite ligands.

In recent years, our lab focused on recycling a variety of precious transition-metal catalysts using polyolefin oligomers as nonpolar polymer supports. An example of this approach would be the development of soluble polymer-supported Grubbs catalysts and Hoveyda-Grubbs catalysts.[42-44] In 2011, we reported the work of using

recyclable PE-bound Hoveyda-Grubbs second generation catalysts in ring closing metathesis (RCM) reactions.[45] We designed and prepared a PE-bound N-heterocyclic carbene (NHC) ligand and the Ru complex **22**. The complex **22** was then examined in RCM reactions that were carried out using 2.5 mol% of the catalyst in toluene at 65 °C (Scheme 16). The results showed that the diene substrates were converted to the desired products within 5 min. After cooling the reaction mixture to room temperature, the complex **22** was quantitatively separated from the product by self-precipitation and was then isolated by filtration. The recovered catalyst was reused up to 10 cycles with no significant change in activity. Compared with the products formed using other Hoveyda-Grubbs second generation catalysts, the product formed using complex **22** was visually uncontaminated with Ru residues, and the ICP-MS analysis showed that only <0.3% of the Ru leached into the product.



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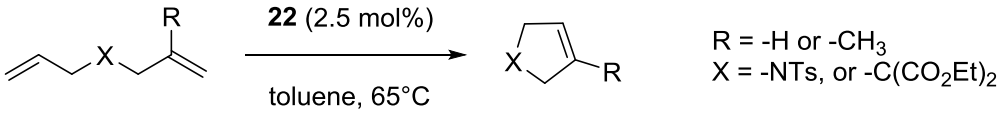
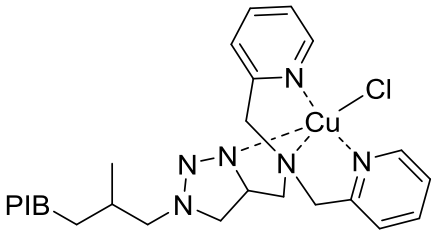


Scheme 16. PE-bound Hoveyda-Grubbs second generation catalyst catalyzed Ring closing metathesis reactions.

Polyisobutylene as a Soluble Polymer Support for Catalyst Recovery

As noted above, polyolefin oligomers have been studied as nonpolar soluble polymer supports for catalyst recycling. However, there are limitations of using PE as a polymer support for homogeneous catalysis because it is insoluble in any solvent at room temperature or below. Hence, an alternative approach using PIB as a nonpolar soluble polyolefin support for transition-metal and organic catalysts recovery was developed.[46-48] PIB is an inexpensive and commercially available material[49] and is widely used as sealants, lubricants, and fuel additives. The vinyl terminated PIB oligomers used as starting materials for ligands are prepared by cationic polymerization of isobutylene.[50] The terminal alkene group of PIB can be modified by chemical transformations to synthesize many useful functional groups[51,52] that are used to form a variety of polymer-supported ligands and catalysts. Another important feature of PIB is that it is phase-selectively soluble in nonpolar organic solvents like hexane, heptane, dichloromethane, toluene, and THF at ambient temperature but is insoluble in polar solvents including methanol, acetonitrile, DMF, and water. This excellent phase-selective solubility makes PIB a useful polymer support for the recycling of homogeneous catalysts. In this approach, the catalyst-containing nonpolar phase and the product-containing polar phase are separated using a biphasic liquid/liquid separation strategy after the reaction, and then the catalyst-containing nonpolar phase is recovered through a facile gravity separation and reused in subsequent cycles. Several examples of using PIB as a soluble polymer support to facilitate catalyst separation and recycling that have been reported by our group are discussed below.



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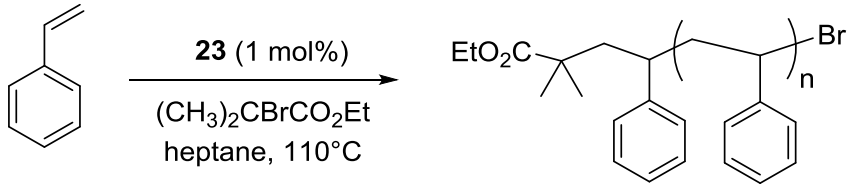


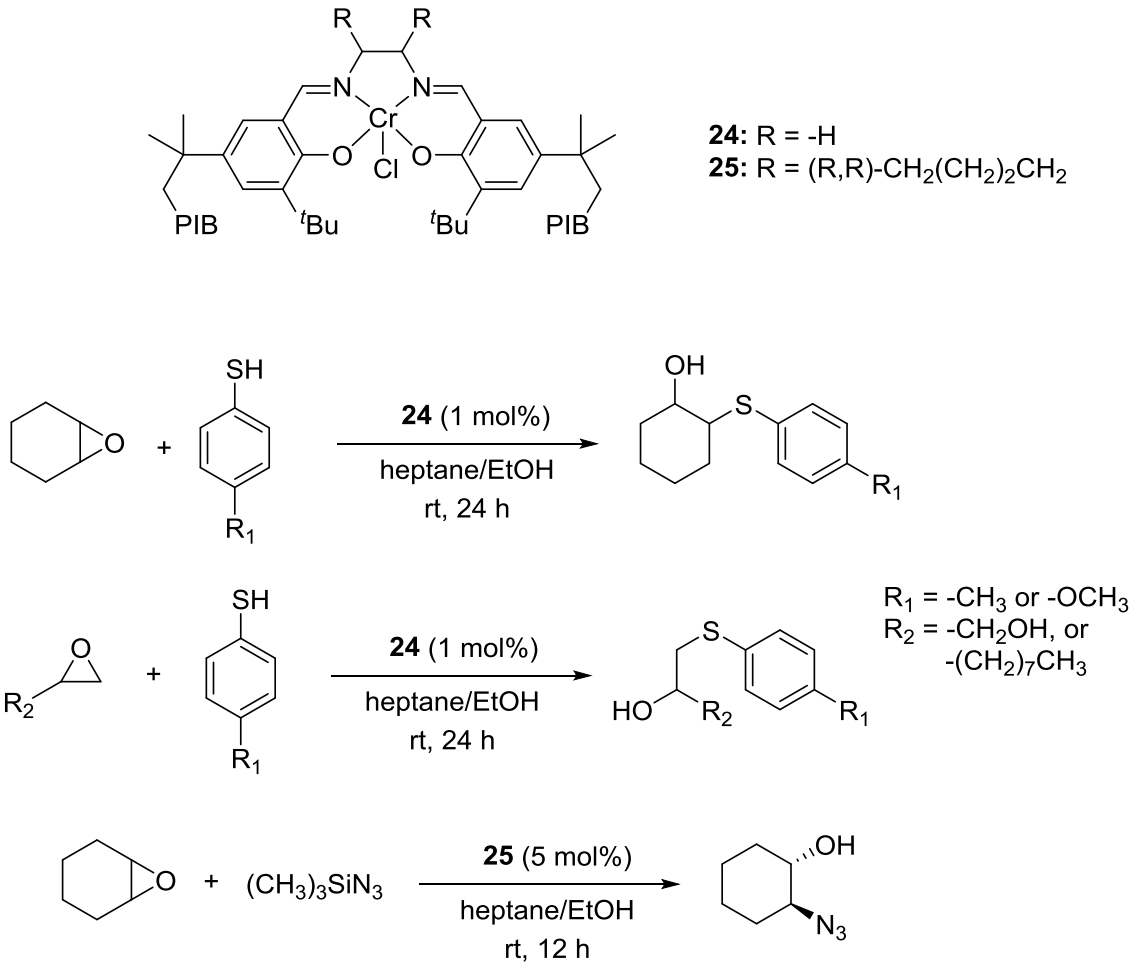
Scheme 17. PIB-bound Cu(I) complex catalyzed ATRP of styrene.

One example of using PIB for catalyst recovery was demonstrated in the work where a PIB-bound Cu(I) complex was used to catalyze an atom transfer radical polymerization (ATRP).[53] In that study, a PIB-bound triazole ligand was prepared using "click" chemistry of an azide-terminated PIB and an alkyne-terminated chelating group, and the ligand was allowed to react with CuCl to produce the PIB-bound Cu(I) complex **23** that showed good phase-selective solubility in heptane. The complex **23** was then used to catalyze radical polymerization of styrene, and the reaction was performed using 1-bromo-1-phenylethane as an initiator in heptane at 110 °C (Scheme 17). The PIB-bound catalyst showed good catalytic activity and the formed polystyrene that is insoluble in heptane precipitated from the solution during the reaction. After the reaction was completed, the reaction mixture was cooled to room temperature, and the catalyst-containing heptane phase was separated from the solid polymer products. The products

were then isolated by filtration, and the catalyst-containing heptane phase was recovered and reused for five cycles with 50% conversion of the monomer for each cycle. The reported Cu leaching in the polymer products was ca. 3% of the charged catalyst based on ICP-MS.

In addition to the thermomorphic solid/liquid separation strategy, we also demonstrated an example of using liquid/liquid biphasic separation strategy to recycle PIB-supported transition-metal catalysts.[54] In that work, the synthesis of recyclable PIB-support salen metal complexes was described, and the PIB-bound Cr(III) complexes **24, 25** were prepared by the reaction of PIB-bound salen ligands with $CrCl_2$. To study their catalytic activity, the complexes **24, 25** were used to carry out ring-opening reactions of epoxides with thiolphenols or azidotrimethylsilane (Scheme 18). The reactions were carried out in a heptane/EtOH solvent mixture at room temperature. The results showed that the PIB-bound complexes were comparable with their low molecular weight analogs in these reactions and afforded the β-hydroxy sulfides in high purity (>95%) without further purification. The PIB-supported catalyst and products were initially in a monophasic solution but the catalyst could be isolated as a heptane solution phase which separated after the addition of a small amount of water to the reaction mixture after the reaction converted the latent initial monophasic mixture of heptane and ethanol to a biphasic mixture. The catalyst-containing heptane phase was recovered by gravity separation and reused in subsequent cycles with fresh substrates and solvent added. Using this method, the PIB-supported salen complexes were recycled for 4 times with no loss in catalytic activity. The ICP-MS analysis of the product from the reaction between

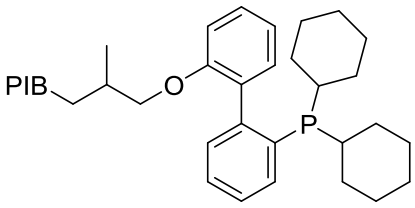
glycidol and 4-methylthiophenol showed the Cr leaching level to be 0.26% of the charged catalyst per cycle.



Scheme 18. PIB-bound Cr(III)-salen complex catalyzed ring-opening of epoxides.

Recent work from our lab described a similar example of using liquid/liquid biphasic separation strategy to recycle a PIB-bound hindered phosphine ligand that was used in Pd(0)-catalyzed C-N coupling reactions.[55] The PIB-bound ligand **26** was

prepared using PIB-bound bromide and hydroxy-substituted dicyclohexylbiaryl phosphine via Williamson ether synthesis. The PIB-bound ligand **26** was examined in Buchwald-Hartwig amination reactions[56] of alkyl or aryl amines and aryl halides in the presence of $Pd(dba)_2$ in heptane at 90°C (Scheme 19). The reactions showed high conversions (>98 %) of the substrates and afforded good isolated yields (82%-94%) of the desired products. After the reaction was completed, the product was isolated from the reaction mixture by extraction with methanol, and the catalyst-containing heptane phase was recovered and reused for five cycles with no loss in activity. The ICP-MS analysis showed that the Pd leaching was 0.1% or 0.02% of the charged catalyst in reactions of bromobenzene with *N*-methylaniline or morpholine, respectively.



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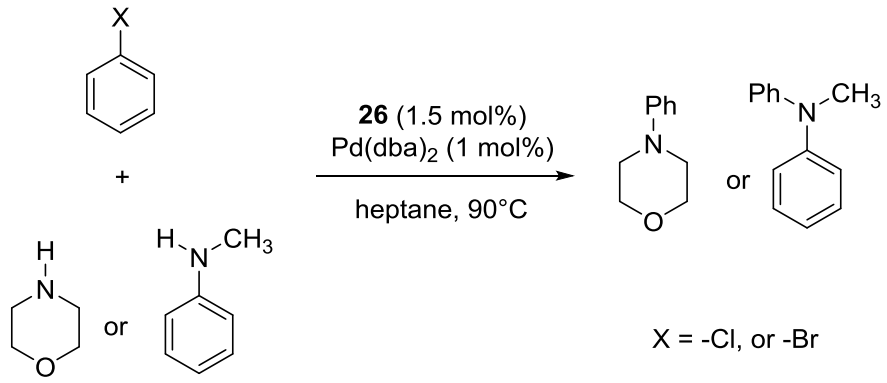

Scheme 19. Pd(0)-catalyzed aryl amination reactions using PIB-bound phosphine ligand.

The research in our group discussed above has mainly focused on the development of green synthetic pathways, especially on better ways to effect the recovery and recycling of transition-metal and organic catalysts after homogeneous reactions. In the following chapters, I will describe in details of the strategies I developed that use PIB as a nonpolar soluble polymer support to synthesize recyclable photoredox catalysts and their applications in visible light-mediated reactions. In addition, novel synthetic methods for carrying out catalytic reactions that take advantage of phase-selectively soluble polymers will also be discussed.

CHAPTER II

USING SOLUBLE POLYMERS TO ENFORCE CATALYST-PHASE-SELECTIVE SOLUBILITY AND AS ANTILEACHING AGENTS TO FACILITATE HOMOGENEOUS CATALYSIS*

Introduction

Soluble polymer supports are useful tools in homogeneous catalysis.[10,57] This work shows that the enforced phase-selective solubility of polyisobutylene (PIB)-supported catalysts can be used to both recycle catalysts and to suppress by-product formation involving the bimolecular reaction of a polar-phase-soluble reactant. Such effects are enhanced using added hydrocarbon polymer cosolvents that can serve as antileaching agents. In this chapter, I will use PIB-bound Rh(II) carboxylate cyclopropanation and X-H (X=O, N, S) insertion catalysts to illustrate these ideas.

Rhodium(II) carboxylates have been widely used as catalysts in cyclopropanation, C-H insertion, X-H (X = O, N, S) insertion, and aromatic cycloaddition reactions of diazo compounds (Scheme 20).[58-63] Extensive work has been focused on recycling of these dirhodium carboxylate catalysts, and both insoluble supported and soluble supported Rh(II) catalysts have been developed and used as recyclable catalysts in these processes.[64-70]

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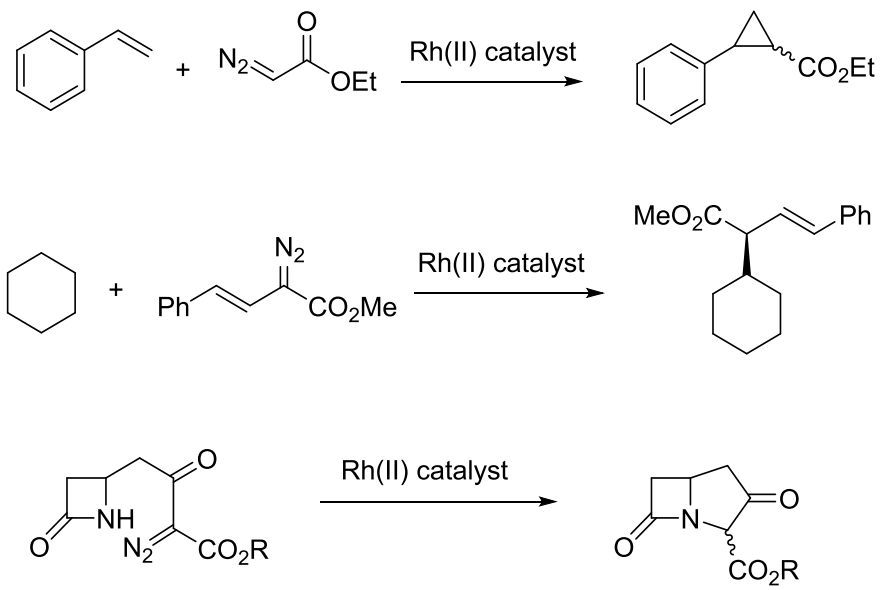
* Reprinted with permission from "Using Soluble Polymers to Enforce Catalyst-Phase-Selective Solubility and as Antileaching Agents to Facilitate Homogeneous Catalysis" by Liang, Y.; Harrell, M. L.; Bergbreiter, D. E. *Angew. Chem. Int. Ed*. **2014**, *53*, 8084-8087, Copyright 2014 by WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.



Scheme 20. Rhodium carboxylates catalyzed reactions.

Davies and coworkers demonstrated an example of using insoluble support to recycle a chiral dirhodium(II) catalyst.[67] In that work, a recoverable and reusable silica-supported Rh_2(*S*-DOSP)$_4$ catalyst **27** (Figure 6) was prepared and examined in a wide range of enantioselective transformations including cyclopropanation, C-H functionalization, and tandem ylide formation/[2,3] sigmatropic rearrangement. The complex **27** showed excellent catalytic activities in these reactions, and the corresponding products were formed in good yields and high ee. After the reaction, the product and catalyst were separated by filtration, and the recovered complex **27** was reused in subsequent cycles with fresh substrates and solvent added through 5 times with no loss in catalytic activity.

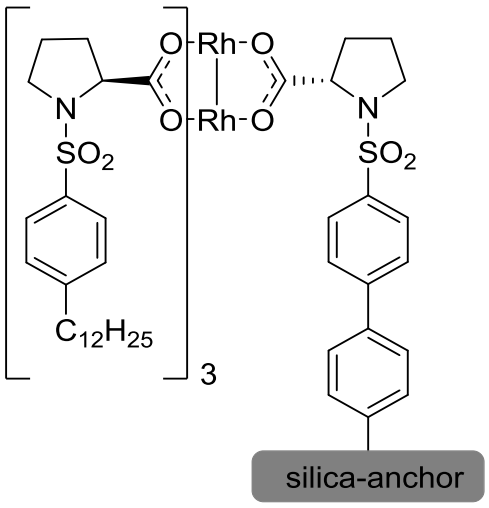


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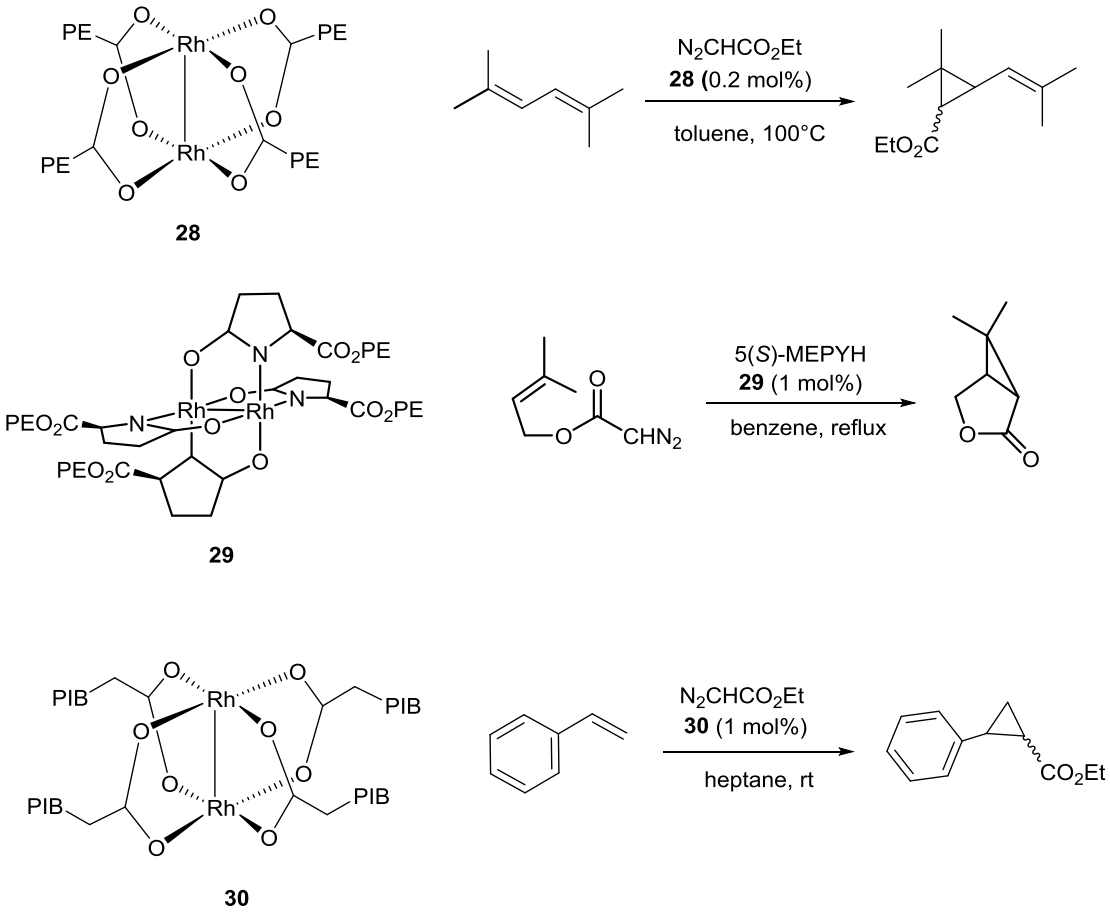
Figure 6. Silica-supported Rh_2(*S*-DOSP)$_4$ catalyst.

The work of using soluble polymer support to recycle the rhodium carboxylate via solid/liquid separation strategy was reported by our group.[68] In that work, a recyclable PE-bound Rh(II) complex **28** was developed, and the catalyst was prepared by the reaction of PE-bound carboxylic acid ligand with $Rh_2(OAc)_4$. To study its catalytic activity, the complex **28** was examined in the cyclopropanation of alkenes with ethyl diazoacetate (N_2CHCO_2Et) in toluene at 100 ˚C (Scheme 21). The results showed that the PE-bound Rh catalyst was comparable with the low molecular weight catalyst and gave the cyclopropanation products in moderate to high yield. After cooling the reaction mixture to room temperature, the complex **28** was recovered by filtration and reused up to 9 cycles with no significant change in reactivity and selectivity. The Rh leaching level was shown to be less than 1% of the charged catalyst. Moreover, the

insertion reactions were also investigated using complex **28**, and the products formed in satisfactory yields.



Scheme 21. PE-bound and PIB-bound Rh(II) complexes catalyzed reactions.

One year later, the work from Bergbreiter and Doyle showed the preparation of a PE-bound Rh(II) 2-pyrrolidone-5(*S*)-carboxylate catalyst, PE-Rh_2(5(*S*)-PYCA)$_4$.[69] The complex **29** was used to carry out intramolecular C-H insertion, intramolecular cyclopropanation and intermolecular cyclopropanation reactions in the presence of

methyl 2-pyrrolidone-5(*S*)-carboxylate (5(*S*)-MEPYH) (Scheme 21). The corresponding products formed in modest yields with good enantioselectivity. After the reaction, the precipitate catalyst was recovered by filtration and reused for 7 times with no significant decrease in catalytic activity.

In 2007, our group demonstrated an example of using PIB as a nonpolar polymer support to recycle the rhodium catalyst.[70] In that work, the synthesis of a PIB-bound Rh(II) complex **30** was achieved through the ligand exchange reaction. The complex **30** was then used to catalyze the cyclopropanation of styrene in heptane at room temperature and afforded the products in satisfactory yields (Scheme 21). After the reaction, the product was extracted from the reaction mixture with either acetonitrile or ethyleneglycol diacetate (EGDA). However, the acetonitrile is preferred because it has a lower boiling point than EGDA; therefore, the product can be isolated more easily. The catalyst-containing heptane phase was then recovered and used to carry out the reaction with fresh substrates added 9 times with no loss of catalytic activity.

These studies showed that the supported Rh(II) complexes have excellent catalytic activity and recyclability. However, all of these reactions that used supported catalysts like reactions that use conventional Rh(II) catalysts require slow addition of the diazo substrate with a syringe pump because of the facile and exothermic Rh(II)-catalyzed dimerization of the diazo reactant (Figure 7).[71] This method limits the applicability of this chemistry in large-scale synthesis in industry. Therefore, developing alternative pathways to perform the reaction without the use of syringe pump addition of

the diazo substrate gained our interest. Our hypothesis was that a new approach would be to carry out the reaction in a liquid/liquid biphasic solvent mixture.

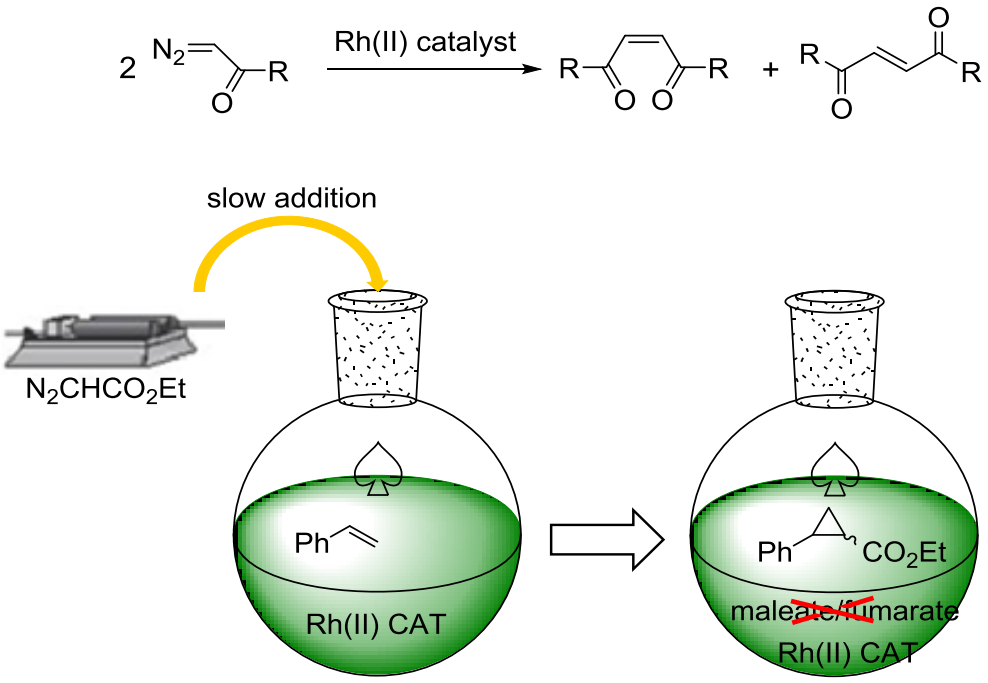
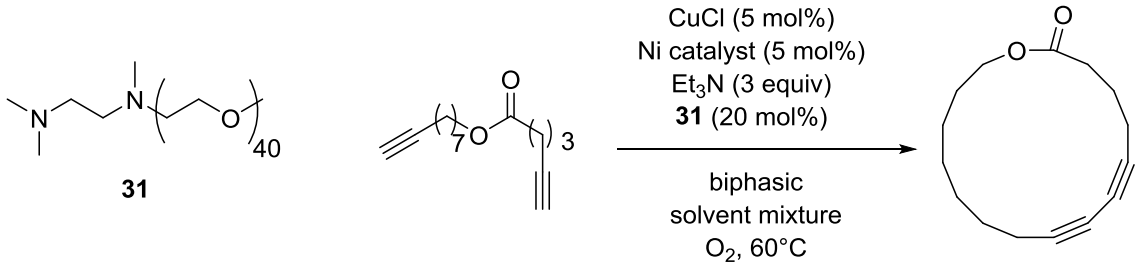


Figure 7. Rh-catalyzed reaction using conventional slow addition method.

The concept of controlling of an unwanted bimolecular reaction in a biphasic system has been reported in other chemistry. Collins and coworkers showed an example of conducting macrocyclizations in biphasic media where catalyst and substrates are separated. In this scheme, the unwanted intermolecular oligomerization can be suppressed without the use of extremely diluted conditions.[72] This was demonstrated using a PEG-bound tetramethylethylenediamine (TMEDA) ligand **31** that allows for the Cu/Ni cocatalyst to be sequestered in the polar phase during the reaction. The

macrocyclic Glaser-Hay coupling of diyne was carried out efficiently using the Cu/Ni cocatalyst system in the presence of **31** in a biphasic solvent mixture (Scheme 22). In compared with the conventional methods, this phase separation strategy allows the reactions to be conducted at higher concentration and afforded the macrocycles in higher yields.



Scheme 22. Macrocyclic Glaser-Hay coupling of diyne using phase separation strategy.

In our study, we demonstrated the feasibility of a similar idea. We thought that a soluble polymer's phase-selective solubility could segregate the Rh(II) catalyst and diazo reactant in nonpolar and polar phases of a biphasic heptane/CH_3CN mixture enabling both catalyst recycling and suppression of dimer formation without syringe pump addition of the ethyl diazoacetate (Figure 8). This is possible because the low solubility of the diazo reactant in the heptane catalyst-containing phase lowers the bimolecular rate of dimer formation more than the rate of cyclopropanation or O-H insertion.

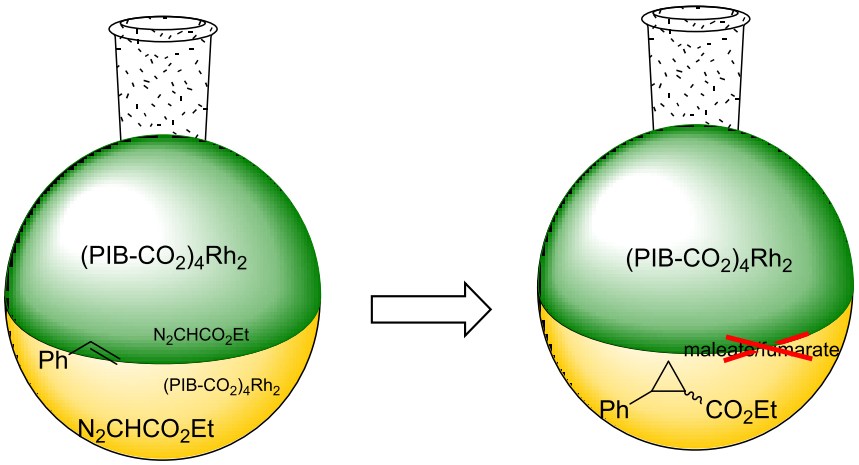
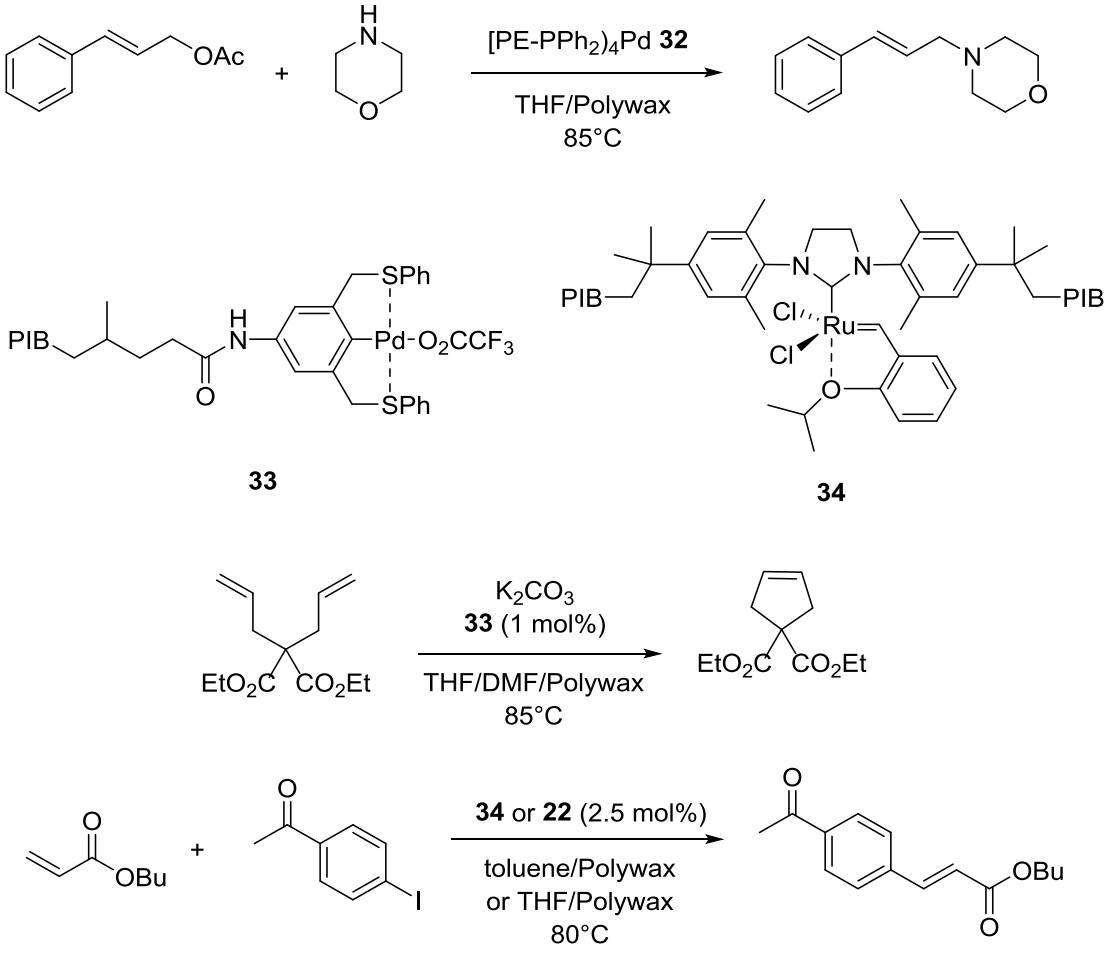


Figure 8. Rh-catalyzed reaction under biphasic heptane/CH_3CN mixture.

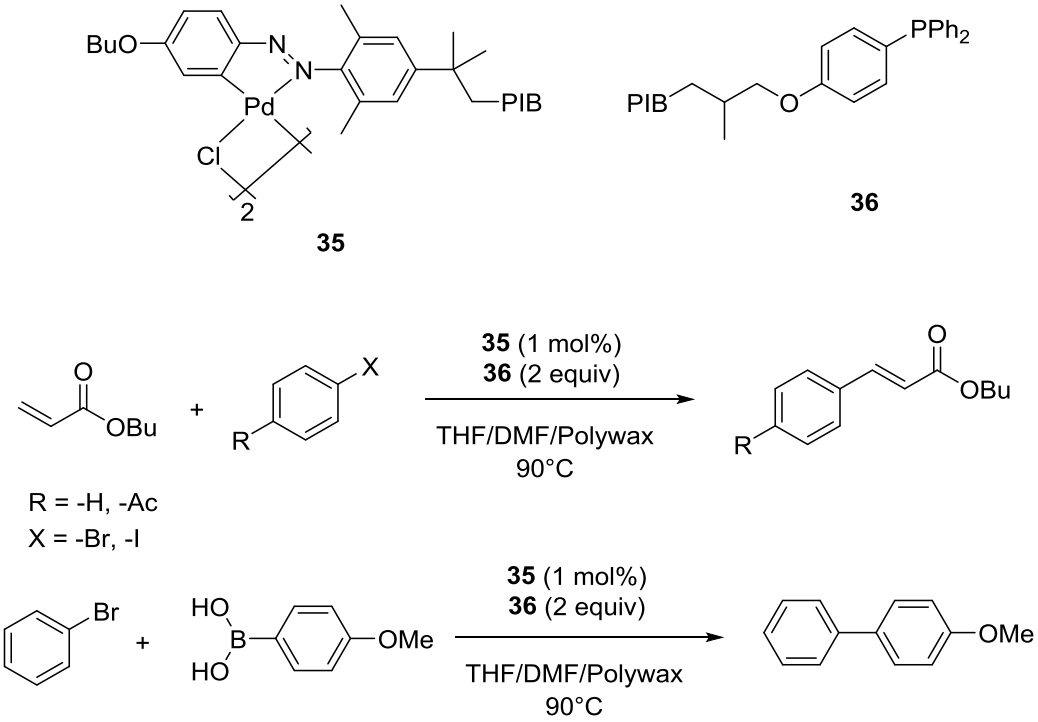
In the past decade, the use of soluble polymers instead of conventional organic solvents as more environmental benign alternative solvents for chemical transformations has been developed.[73-76] A recent report from our group described an example of applying low molecular weight PE wax (Polywax) as an inexpensive, nontoxic, and nonvolatile solvent in homogeneous catalysis.[77] In this report, a variety of soluble-polymer supported catalysts including PE-bound Pd catalyst **32**, PIB-bound Pd catalyst **33**, PE-bound Hoveyda-Grubbs catalyst **22**, and PIB-bound Hoveyda-Grubbs catalyst **34** were investigated (Scheme 23). Allylic substitution, cross-coupling, and ring-closing metathesis reactions were successfully performed under homogeneous conditions using Polywax/THF, Polywax/THF/DMF, or Polywax/toluene solvent mixtures, respectively. The separation was accomplished by addition of water to the reaction to form a liquid/liquid biphasic mixture. After cooling the mixture to ambient temperature, the catalyst-containing Polywax phase can be isolated as solid and reused in subsequent

cycles. The study illustrated that polyolefin oligomers are not only function as catalyst supports but also serve as green solvents for homogeneous catalysis in which the facile separation of the polymer-supported catalyst from the product after a reaction can be achieved.



Scheme 23. Homogeneous catalytic reactions and separation of soluble polymer-supported catalysts using Polywax as a cosolvent.

One year later, we reported the work of using Polywax as a cosolvent to reduce catalyst leaching in homogeneous catalysis.[78] In this case, a recyclable PIB-azobenzene Pd complex **35** was prepared and was used for carbon-carbon cross coupling reactions (Scheme 24). The reactions were initially conducted in the heptane/DMF thermomorphic system. The desired products were formed in satisfactory yields, but the Pd leaching into



Scheme 24. Using Polywax as a cosolvent in cross-coupling reactions to reduce palladium leaching.

the product phase was shown to be 7% of the charged catalyst. In order to reduce the leaching, Polywax was introduced as a cosolvent, and the reactions were performed in the Polywax/THF/DMF solvent mixture. The results showed that the Pd leaching level

was significantly dropped to 1.2%. Further studies showed that carrying out the reactions in the presence of a PIB-bound phosphine ligand **36** in the same solvent system further decreased the Pd leaching to 0.12%. The study suggested that using polyolefin solvents in catalytic reactions can be an efficient strategy to minimize catalyst leaching into the product phase.

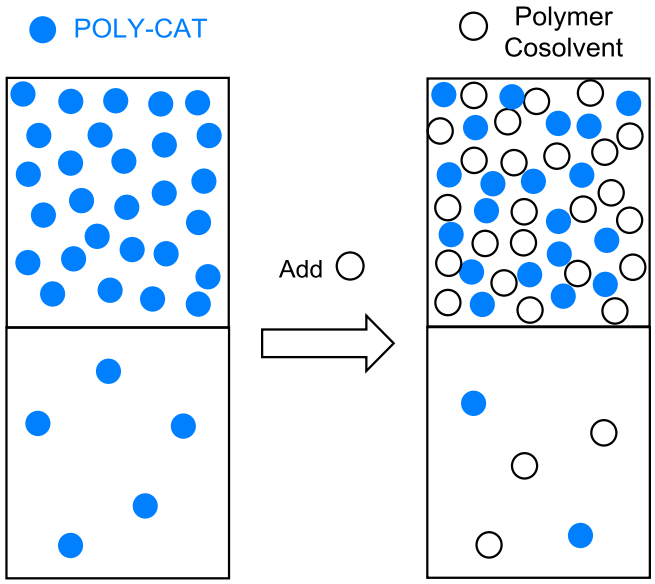


Figure 9. Adding soluble polymer cosolvents as antileaching agents in a liquid/liquid biphasic solvent mixture.

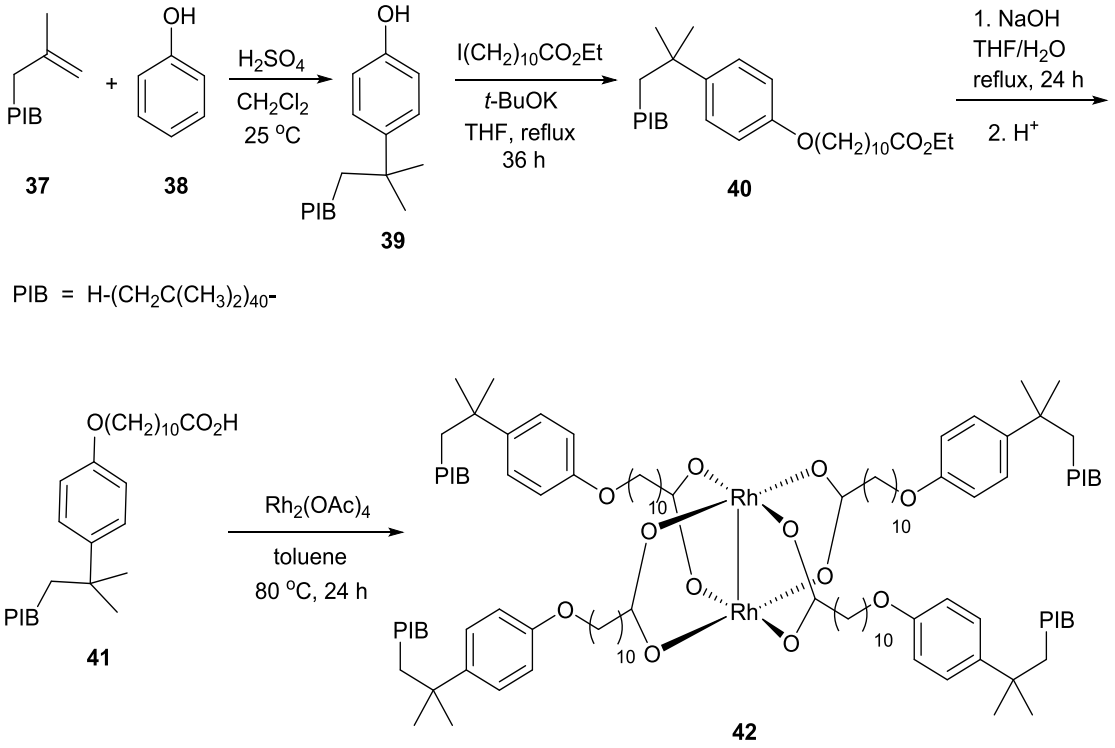
In this work, we further explored the application of unfunctionalized hydrocarbon polymers as cosolvents using the reaction Figure 8 as a test case. Our results described below showed that adding polyolefin oligomers to the heptane phase of a heptane/polar solvent biphasic mixture limits both dimer formation and leaching of PIB-bound species into the polar phase of a heptane/polar solvent biphasic mixture as

suggested by the cartoon in Figure 9. These results suggest new roles for soluble polymers or oligomers as supports or as cosolvents in catalysis where soluble polymer supports recycle catalysts,[73] suppress undesired side reactions and reduce leaching of heptane-soluble polymer-bound species.

Results and Discussion

A PIB-supported heptane-soluble Rh(II) catalyst was prepared as shown in Scheme 25. This route to a $[(PIB_{2300}\text{-}CO_2)_2Rh]_2$ catalyst was more convenient for multigram syntheses than a previous one,[70] which involves the use of a strong oxidant $KMnO_4$ that can cause safety concerns in large-scale synthesis. Using vinyl-terminated PIB_{2300} **37** as the starting material, the PIB-bound phenol **39** was prepared following the literature procedures.[51] It was then allowed to react with ethyl 11-iodoundecanoate in refluxing THF to generate the ester **40**. The ester was hydrolyzed to afford the PIB-bound carboxylic ligand **41** which was used to form the Rh catalyst **42** by ligand exchange with $Rh_2(OAc)_4$ in toluene at 80 °C. The product **42** was a dark green viscous oil which was characterized by UV/Vis spectroscopy. A Rh loading of 0.167 mmol/g in **42** was determined based on the absorbance at 588 nm (λ_{max}) of a known amount of **42** in EtOH/toluene and the molar absorptivity ε of $Rh_2(OAc)_4$ in this same solvent mixture ($\varepsilon = 260\ M^{-1}\,cm^{-1}$, $\lambda_{max} = 587$ nm). In this case, we assumed that the PIB-bound Rh(II) complex **42** has the same ε as the $Rh_2(OAc)_4$ in the same solvent system. These spectral data are comparable to the reported data for $Rh_2(OAc)_4$ in octanol ($\lambda_{max} = 585$ nm, ε =

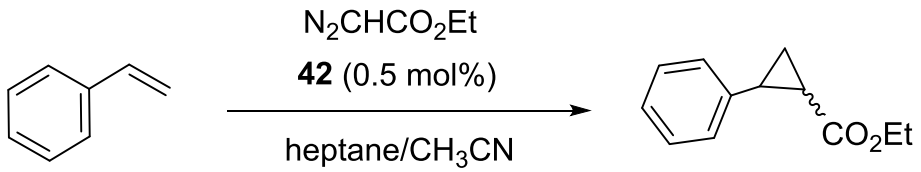
298 $M^{-1}cm^{-1}$).[79] The green PIB_{2300}-bound Rh(II) carboxylate complex was visually insoluble in acetonitrile.



Scheme 25. Synthesis of a PIB-bound carboxylic acid and its use in the formation of a PIB-bound Rh(II) catalyst.

The studies in this work make use of the phase-selective solubility of **42** and the fact that ethyl diazoacetate is relatively insoluble in heptane versus acetonitrile to facilitate cyclopropanation and O-H insertion catalytic reactions of **42**. We first confirmed that the PIB-bound Rh complex **42** was effective in cyclopropanation of styrene in CH_2Cl_2 using syringe pump addition of ethyl diazoacetate to minimize the

maleate/fumarate dimer formation. This reaction produced a 71% yield of the 2-phenyl-1-cyclopropylcarboxylic acid ester as a 67/33 *trans/cis* mixture with 2.3% of the carbene dimer. These results are comparable to previous results with soluble polymer-bound Rh(II) catalysts that used syringe pump addition of the ethyl diazoacetate to suppress carbene dimer formation.[68,70] Next, we examined **42** as a recyclable catalyst for cyclopropanation of styrene with ethyl diazoacetate under biphasic conditions without the use of a syringe pump. In this case, most of the ethyl diazoacetate was in the acetonitrile phase. The reaction was carried out in a heptane/CH_3CN biphasic system at room temperature using 0.5 mol% of **42** (Scheme 26).



Scheme 26. Cyclopropanation of styrene catalyzed by the PIB-bound Rh carboxylate catalyst **42** in a biphasic heptane/CH_3CN solvent mixture at 25 ˚C.

Under these conditions, **42** was successfully reused affording the cyclopropanation product in 66, 67, and 74% yield (as a ca. 67/33 *trans/cis* mixture) in cycles 1-3. The yield of dimer by-product was 7.7, 7.1, and 6.7% for these same three cycles (as a 61/39 *Z/E* mixture) (Table 1). The catalyst **42** was recycled by separating the heptane phase containing **42** from the acetonitrile product phase and reusing the heptane solution in another cycle. The average yield of the isolated cyclopropanation product

was 65%/cycle. These results show that phase isolation of a PIB-bound Rh(II) catalyst from ethyl diazoacetate suppresses the dimerization of diazo substrates while still affording typical products in a reasonable time frame.

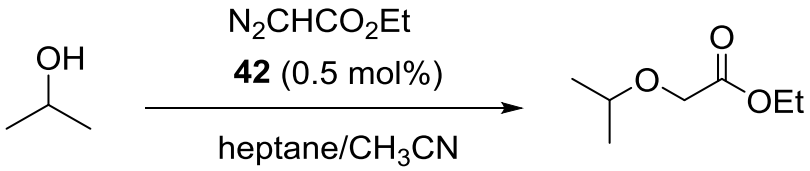
Table 1. Results of styrene cyclopropanation reaction catalyzed by **42** using biphasic conditions to effect the ethyl diazoacetate dimerization suppression.[a]

Polyolefin Cosolvent	Cycle	Yield [%][b]	Dimer Yield [%][b, c]
CH_2Cl_2[d]	-	71[e]	2.3
None	1	66	7.7
None	2	67	7.1
None	3	74	6.7
PIB_{2300}[f]	1	61	3.8
PIB_{2300}[f]	2	58	4.5
PIB_{2300}[f]	3	64[g]	5.4

[a]2 mmol scale reactions with 0.5 mol% of **42** and 20 mmol of styrene at 25 ˚C using a 5 mL/15 mL mixture of heptane/CH_3CN. [b]Yields are based on ^{1}H NMR spectroscopy. [c]A mixture of maleate/fumarate products. [d]Syringe pump addition was used to suppress N_2CHCO_2Et dimerization in this CH_2Cl_2 monophasic reaction. [e]Yield of isolated product. [f]PIB_{2300} was added as a cosolvent. [g]Combining the products of three cycles in which PIB was present afforded 0.67 g of the cyclopropanation product.

We thought that the low amount of dimer formation under biphasic conditions could be due to two factors: the enforced phase-selective solubility of **42** in the heptane phase of the heptane/CH_3CN biphasic mixture and the relatively low concentration of

ethyl diazoacetate in the catalyst-rich heptane phase. The low concentration of catalyst in the acetonitrile phase, in which there is a high concentration of ethyl diazoacetate, slows dimer formation in acetonitrile whereas the low concentration of ethyl diazoacetate in heptane slows what would otherwise be a fast bimolecular dimer reaction in the catalyst-rich heptane phase. Both effects could also act synergistically.



Scheme 27. O-H insertion of isopropanol catalyzed by the PIB-bound Rh carboxylate catalyst **42** in a biphasic heptane/CH_3CN solvent mixture at 25 ˚C.

In addition to cyclopropanation, rhodium carbenoids generated from diazo compounds are also used to insert a carbene equivalent in X-H bonds. This reaction can also be effected by phase-segregated catalyst **42** in a heptane/CH_3CN biphasic mixture without the need for syringe pump addition of ethyl diazoacetate to suppress maleate/fumarate dimer formation (Scheme 27). As shown in Table 2, **42** was successfully recovered and reused through three cycles of an O-H insertion into isopropyl alcohol affording the product in a 63% average yield/cycle. The average yield of dimers was 6.6%, a result similar to that obtained using syringe pump addition with **42** as a catalyst in monophasic CH_2Cl_2.

Table 2. Results of O-H insertion of isopropyl alcohol catalyzed by **42** using biphasic conditions to effect the ethyl diazoacetate dimerization suppression.[a]

Cycle	Yield [%][b]	Dimer Yield [%][c]
1	72	6.4
2	66	6.8
3	51	6.6
-[d]	65	4.1
-[e]	66	2.6

[a]2 mmol scale reactions with 0.5 mol% of **42** and 20 mmol of isopropanol at 25 ˚C using a 5 mL/15 mL mixture of heptane/CH_3CN. [b]Average ^1H NMR spectroscopy yields of product from two independent runs. [c]NMR yield of the by-product (a ca. 60/40 *Z/E* mixture). [d]An O-H insertion reaction carried out in the presence of added unfunctionalized PIB. [e]An O-H insertion carried out in CH_2Cl_2 adding N_2CHCO_2Et with a syringe pump.

Our hypothesis noted above was that the small amount of dimer formed results either from minimal catalyst **42** leaching into the ethyl diazoacetate-rich acetonitrile phase, from a lowered ethyl diazoacetate concentration in the heptane phase, or from a combination of these scenarios. Thus, we expected that we could further reduce by-product formation either by reducing the leaching of **42** into acetonitrile or by further reducing the concentration of ethyl diazoacetate in the heptane phase and we set out to test that notion using unfunctionalized PIB as an additive.

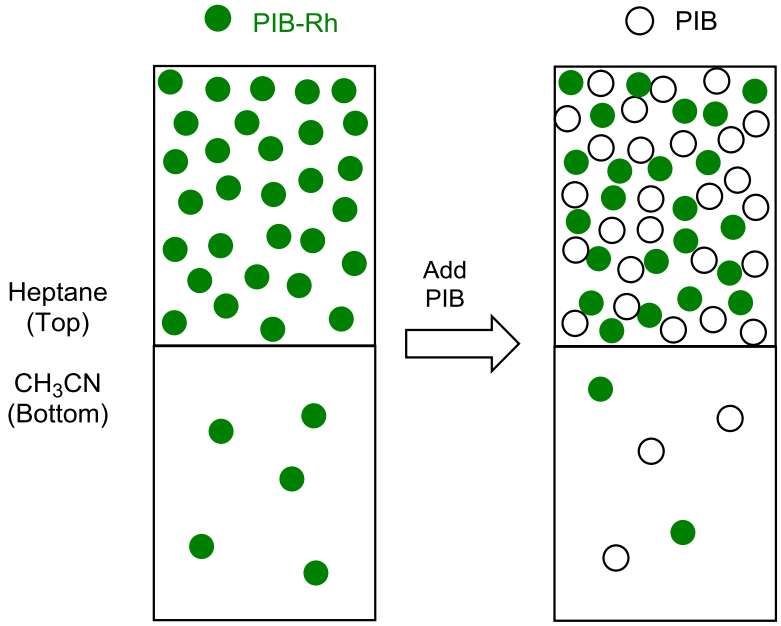


Figure 10. Adding polyolefin cosolvents as antileaching agents in a liquid/liquid biphasic solvent mixture.

The first scheme we explored was to add an unfunctionalized polyolefin as cosolvent to the heptane phase. The premise was that addition of unfunctionalized PIB would competitively saturate the acetonitrile phase, thereby reducing the amount of **42** in that phase (Figure 10). Our initial idea was to test this idea by looking physically for leaching. However, there was no visually apparent leaching of **42** into acetonitrile under any conditions so this idea was instead tested by examining how added hydrocarbon polymer cosolvents reduced the leaching of two chromogenic PIB derivatives **43** and **44** that had visible leaching (Figure 11).

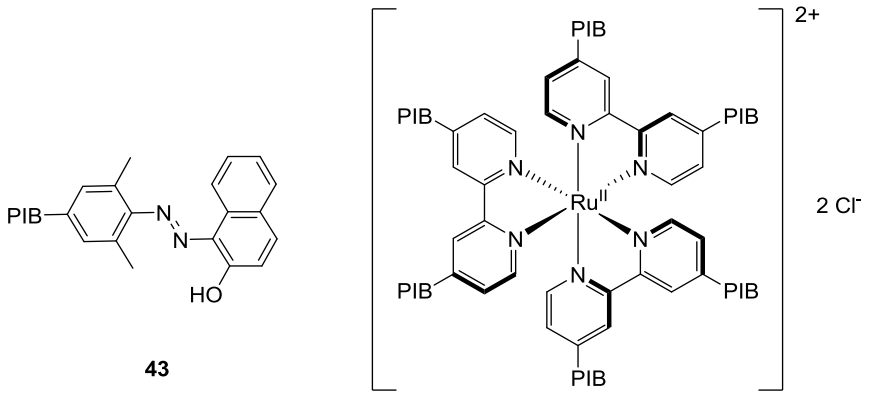


Figure 11. PIB-bound azo dye and PIB-bound Ru(II)-bipyridine complex.

The first study of the antileaching effect of added hydrocarbon cosolvents used the PIB_{2300}-bound azo dye **43**.[80] The dye was dissolved in 3.0 g of heptane, aPP,[81] or a heptane/aPP solvent mixture (2:1 wt:wt). After dissolution of the dye in the nonpolar solvent, 3.0 g of methanol was added and the biphasic solvent system was heated to 90 ˚C with stirring to fully or partially (in the case of aPP) miscibilize the nonpolar solvent with methanol. Then the solution was cooled to room temperature and a biphasic system was reformed. The methanol layer was analyzed by UV-visible spectroscopy to determine leaching of **43**. The results showed the highest leaching for the heptane/methanol solvent system with an absorbance of 0.36 at 492 nm (blue curve on Figures 12). The leaching of **43** decreased by ca. 30% in the heptane/aPP/methanol solvent system, and the absorbance in methanol was 0.25 (purple curve on Figures 12). Over a 50% decrease in leaching was observed in the aPP/methanol solvent system, and the absorbance of **43** in methanol was 0.16 (red curve on Figures 12). The leaching of

the dye can also be visualized in picture that is shown in Figure 13, and there was less leaching observed in polar phase of the aPP/methanol solvent system (right) than the heptane/methanol solvent system (left). In the case of aPP/methanol solvent system, the aPP phase is denser than the methanol phase.

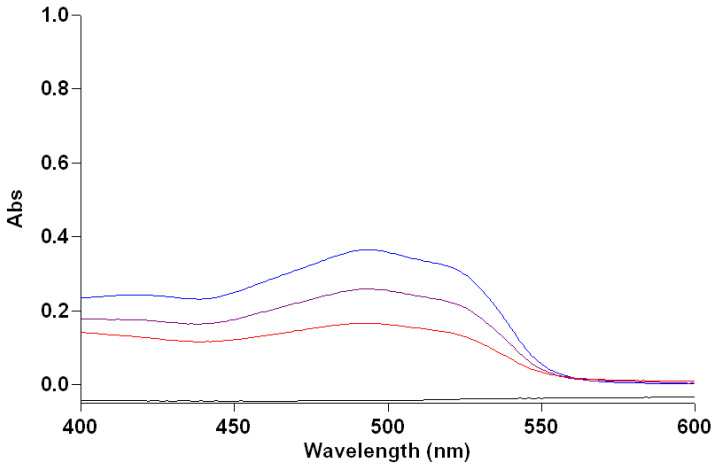


Figure 12. UV-visible spectra of the PIB-bound azo dye **43** in methanol.

Figure 13. Leaching of the PIB-bound azo dye **43** into the polar phase of a biphasic system.

Studies with a chromogenic PIB-bound Ru(II)-bipyridine complex **44** used in my earlier work (cf. Chapter III) as a photoredox catalyst[82] showed that the antileaching effect of added hydrocarbon copolymers on soluble PIB-bound dyes also affects PIB-bound metal complex leaching. Dissolving **44** in a thermomorphic heptane/ethanol/DMF (4/2/3 vol/vol/vol) system forms a monophasic solution at 90 ˚C that becomes biphasic on cooling to 25 ˚C. Reheating and adding 0.4 g of PIB_{2300} to the hot monophasic mixture and cooling this solvent mixture to reform a biphasic mixture at 25 ˚C visually decreasing the leaching of **44** into the polar phase (Figure 14).

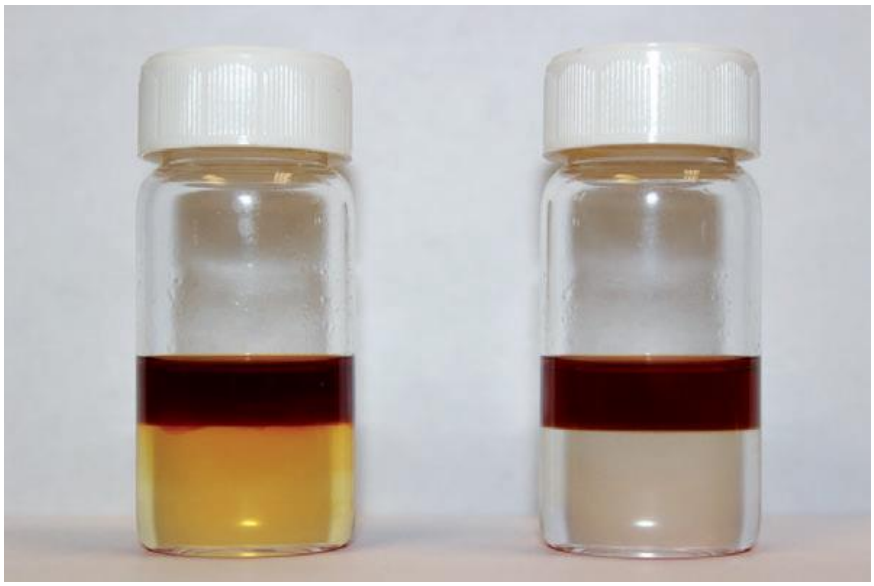


Figure 14. Antileaching effect of PIB_{2300} for the PIB-bound Ru(II)-bipyridine complex **44** in a heptane/ethanol/DMF solvent system; no PIB (left) or 0.45 g of added PIB_{2300} in 4 mL of a heptane phase containing 80 mg of **44** (right).

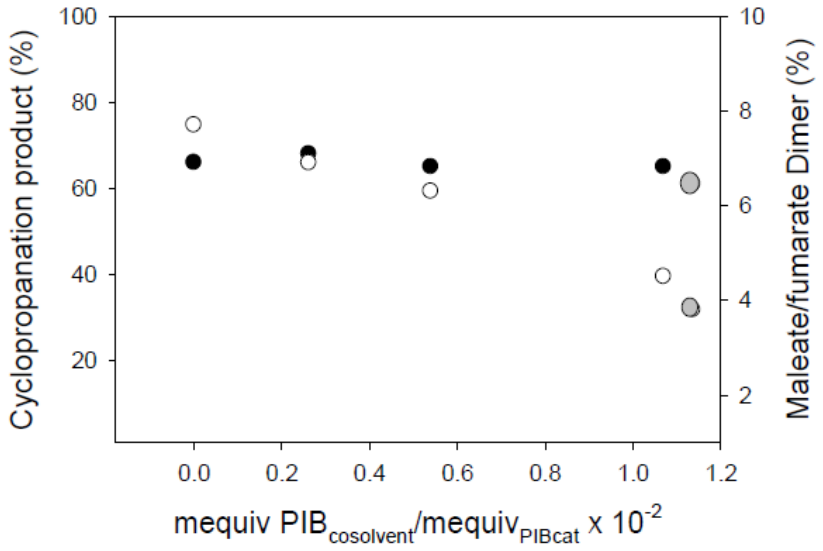


Figure 15. Effects on ^{1}H NMR spectroscopy yields for styrene cyclopropanation and N_2CHCO_2Et dimer showing suppression of dimer formation due to the addition of PIB_{1000} to a heptane/CH_3CN biphasic reaction at 25 ˚C using 0.5 mol% of **42** as a catalyst. The open circles correspond to the amount of dimer by-product (the right axis). The closed circles correspond to the amount of cyclopropanation product. The greyish points correspond to the cyclopropanation product and dimer formed when PIB_{2300} was added.

Next, we carried out a series of experiments in which PIB was added as a cosolvent to reduce by-product formation in cyclopropanation and O-H insertion. The results are listed in Tables 1 and 2. In cyclopropanation, average dimer yields through three cycles of a catalytic reaction decreased from 7.4% without any addition of PIB to 4.6% with PIB_{2300} as the cosolvent. Similar results for dimer formation were obtained with PIB_{2300} as the cosolvent in O-H insertions (Table 2). The reduction of dimer

formation linearly correlated with the amount of added PIB. PIB_{1000} was comparable in effect to PIB_{2300} (Figure 15). A small decrease in the cyclopropanation product yield was also noted.

The addition of PIB cosolvent could reduce by-product formation either by lowering the leaching of **42** into acetonitrile or by reducing the concentration of ethyl diazoacetate in the heptane phase. The decrease in yield for the cyclopropanation product suggested the latter explanation. This was confirmed by analyses showing that the ethyl diazoacetate concentration in heptane decreased from 5.0×10^{-3} to 3.2×10^{-3} to 2.5×10^{-3} M as the amount of added PIB in heptane increased from 0 to 0.07 to 0.22 M.

Suppression of dimer formation due to a lowered concentration of **42** in the ethyl diazoacetate-rich acetonitrile phase could be an alternative explanation for decreased dimer byproduct in experiments where PIB is added as a cosolvent. Hence, studies of the dimerization of ethyl diazoacetate by $Rh_2(OAc)_4$ or **42** under monophasic and biphasic conditions were investigated. We first carried out a reaction of ethyl diazoacetate using **42** in in heptane/acetonitrile biphasic system, and aliquots of acetonitrile phase were analyzed by ^{1}H NMR spectroscopy. The result showed that dimerization occurred slowly in the biphasic system. Then we carried out this reaction using $Rh_2(OAc)_4$ in acetonitrile to see if a significant amount of dimers would form in this monophasic condition. However, the result showed that dimerization of ethyl diazoacetate only proceeds to 16% after 10 h at 25 ˚C. In contrast, ethyl diazoacetate in dichloromethane homogeneous system quantitatively dimerized with 0.5 mol% of either $Rh_2(OAc)_4$ or **42** at 25 ˚C within 10 min. These experiments indicated that even if **42** were to leach into the

acetonitrile phase, it would not produce much dimer. While added PIB cosolvent could decrease leaching of **42** into acetonitrile, the antileaching effect of PIB is not the primary reason for the lower dimer byproduct formation. As a result, a lowered concentration of **42** in the acetonitrile phase was less important than a decrease in the ethyl diazoacetate concentration in the heptane phase in accounting for the effect of PIB cosolvent addition.

Conclusions

In conclusion, this work describes new roles for soluble polymer-bound catalysts and soluble polymers in homogeneous catalysis. Using a recyclable Rh(II) cyclopropanation/O-H insertion catalyst as an example, we show how the phase-enforced solubility of a polymer support can suppress the undesired bimolecular dimerization reaction of ethyl diazoacetate in a heptane/CH_3CN biphasic reaction mixture without recourse to the use of syringe pump addition to maintain a low ethyl diazoacetate concentration. We show that adding a hydrocarbon polymer as a cosolvent further suppresses the formation of by-products from ethyl diazoacetate dimerization. These experiments also show that added hydrocarbon polymers in biphasic nonpolar/polar liquid/ liquid solvent mixtures act as antileaching agents. This effect of hydrocarbon polymer cosolvents could be a general and inexpensive way to minimize the leaching of precious catalysts or ligands during liquid/liquid biphasic separations.

CHAPTER III

VISIBLE LIGHT MEDIATED PHOTOREDOX REACTIONS CATALYZED BY RECYCLABLE PIB-BOUND RUTHENIUM PHOTOREDOX CATALYSTS*

Introduction

In recent years, the development of environmentally benign synthetic pathways has become increasingly important. Photochemistry and photocatalysis are examples of such chemistry. Catalytic reactions that use visible light as a sustainable, abundant, and environmentally benign energy source have recently received heightened attention with the development of new homogeneous organo- and metal photocatalysts for such transformations.[83,84] For example, ruthenium and iridium polypyridyl complexes (Figure 16) have received attention as new photoredox catalysts due to their high stability, long excited state lifetime, and excellent photoredox properties.[85-87] The reactivity of these catalysts and their application to a number of visible light induced reactions by groups including those of MacMillan,[88-90] Stephenson,[91-93] Yoon[94-96] and others[97-102] have shown the applicability of such catalysts to diverse chemistry including C-H functionalization, reductive dehalogenation, polymerizations, and cycloadditions. These synthetically useful transformations are highlighted by their mild reaction conditions, excellent catalytic activities, and avoid the use of hazardous reagents.

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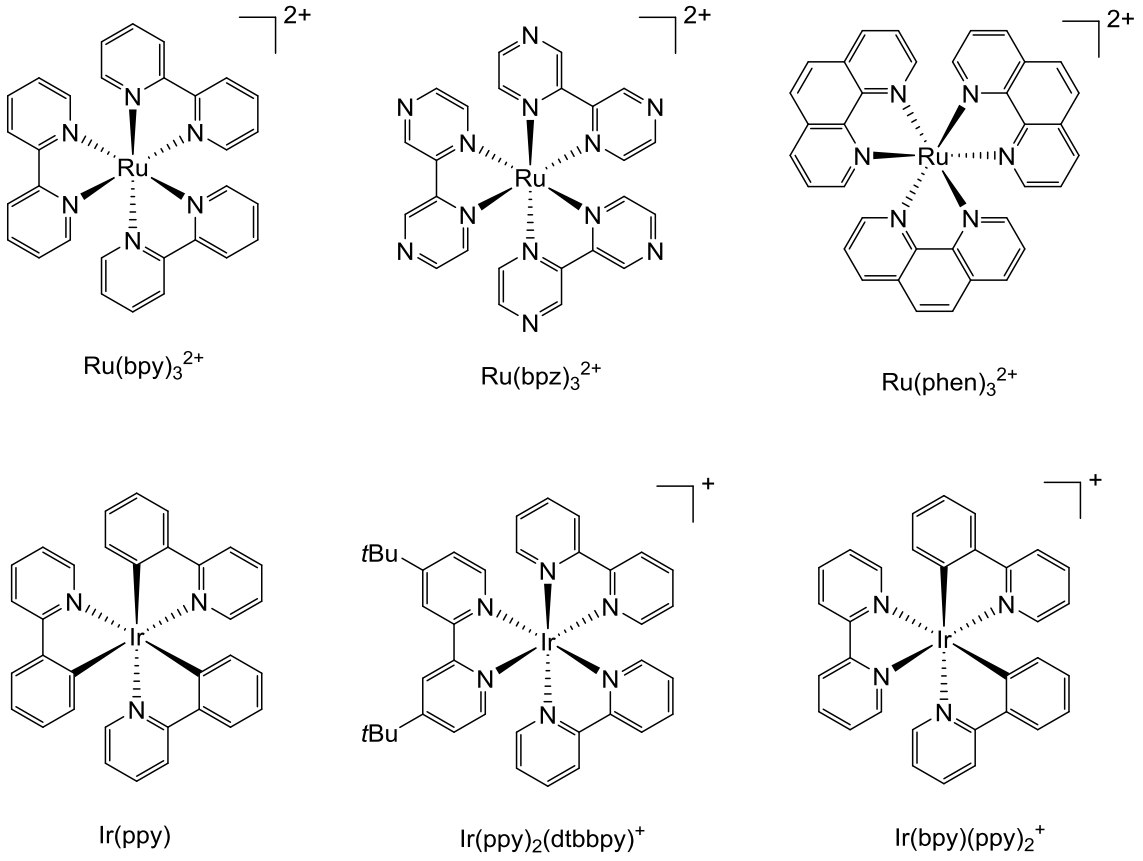
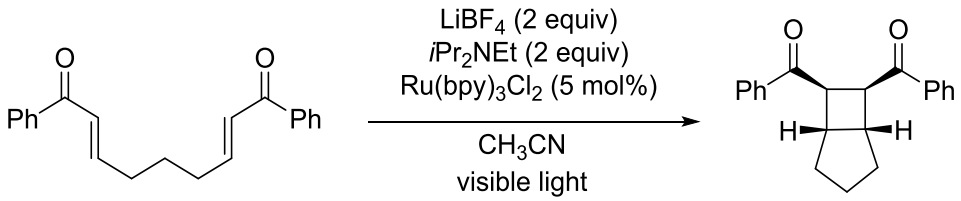


Figure 16. Ruthenium and iridium photoredox catalysts.

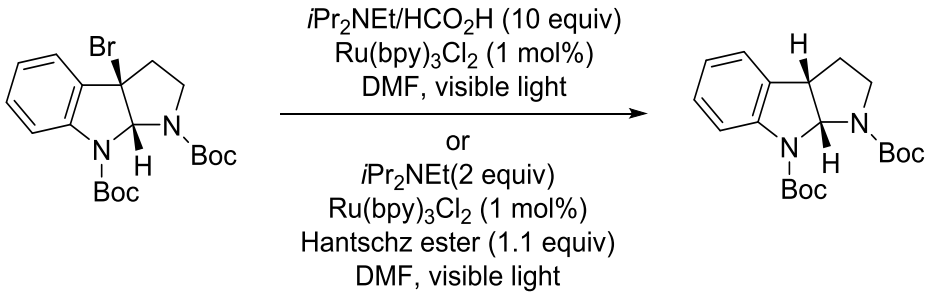
In 2008, Yoon and coworkers reported the work of using $Ru(bpy)_3Cl_2$ photoredox catalyst to conduct [2 + 2] cycloaddition of bis(enones) (Scheme 28).[94] The reactions were conducted using 5 mol% of $Ru(bpy)_3Cl_2$ in the presence of *i*Pr_2NEt, and $LiBF_4$ in acetonitrile under light irradiation. Bis(enone) substrates with various functional groups were examined and showed good reactivity in this condition. Intermolecular cycloaddition of aryl enones also afforded the products in satisfactory yields with high diastereomeric ratio (dr). A mechanism study indicated that light irradiation of $Ru(bpy)_3^{2+}$ generates an excited state $Ru(bpy)_3^{2+*}$ that is reduced by *i*Pr_2NEt to produce

the $Ru(bpy)_3^+$, and the $Ru(bpy)_3^+$ complex can transfer electron to the lithium activated bis(enone), followed with the initiation of the cycloaddition.



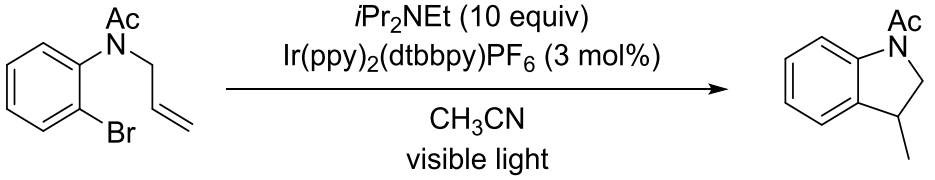
Scheme 28. [2 + 2] cycloaddition using $Ru(bpy)_3Cl_2$ photoredox catalyst.

A tin-free visible light-mediated reductive dehalogenation was developed by Stephenson and coworkers.[91] The reactions were examined in two different conditions, either using 1.0 mol% of $Ru(bpy)_3Cl_2$, *i*Pr_2NEt and HCO_2H or $Ru(bpy)_3Cl_2$, *i*Pr_2NEt and Hantschz Ester in DMF (Scheme 29). Both conditions are shown to be efficient for reductive dehalogenation of carbon-halogen bond in the presence of various functional groups and afforded the dehalogenation products in high yields. Excellent selectivity and protecting group tolerance were also observed using this method.



Scheme 29. Reductive dehalogenation using $Ru(bpy)_3Cl_2$ photoredox catalyst.

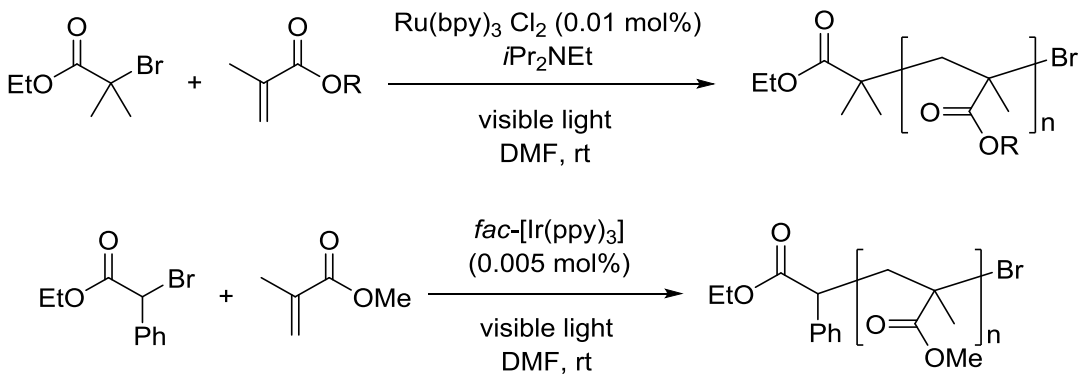
Kim *et al.* described an example of iridium-catalyzed photoredox reductive cyclization and hydrodehalogenation reactions (Scheme 30).[100] in that case, reactions were carried out using 3 mol% $[Ir(ppy)_2(dtbbpy)]PF_6$ in the presence of *i*Pr_2NEt in acetonitrile at ambient temperature under the irradiation of a 20 W CFL or a 2 W blue LED strip. The results showed that a broad range of alkyl and aryl halide substrates undergo photoredox radical cyclization to form the corresponding heterocyclic products in excellent yields.



Scheme 30. Visible light-induced reductive cyclization using iridium photoredox catalyst.

In addition to the low molecular weight organic molecules synthesis, these photoredox catalysts also showed good catalytic activities in polymerization chemistry. In 2011, Choi and coworkers developed a method of visible light-mediated free radical polymerization of methacrylates (Scheme 31).[101] Reactions were performed using $Ru(bpy)_3Cl_2$ with initiator ethyl 2-bromoisobutyrate (EB*i*B), monomers, and *i*Pr_2NEt in DMF at room temperature under light irradiation. Various methacrylate monomers were investigated, and the polymers were formed in satisfactory yields with modest control over the molecular weight.

Later, Hawker and coworkers described a similar example of photocontrolled radical polymerizations using *fac*-Ir(ppy)$_3$ as the catalyst.[102] In that case, polymerization of methyl methacrylate was carried out using 0.005 mol% of *fac*-Ir(ppy)$_3$ catalyst and initiator bromophenylacetate in DMF under the irradiation of a 50W fluorescent lamp. This polymerization process was highly responsive to light and generated the polymer product with excellent control over the molecular weight. These studies showed that photoinitiated polymerization processes provide environmental benign pathways for polymer synthesis.



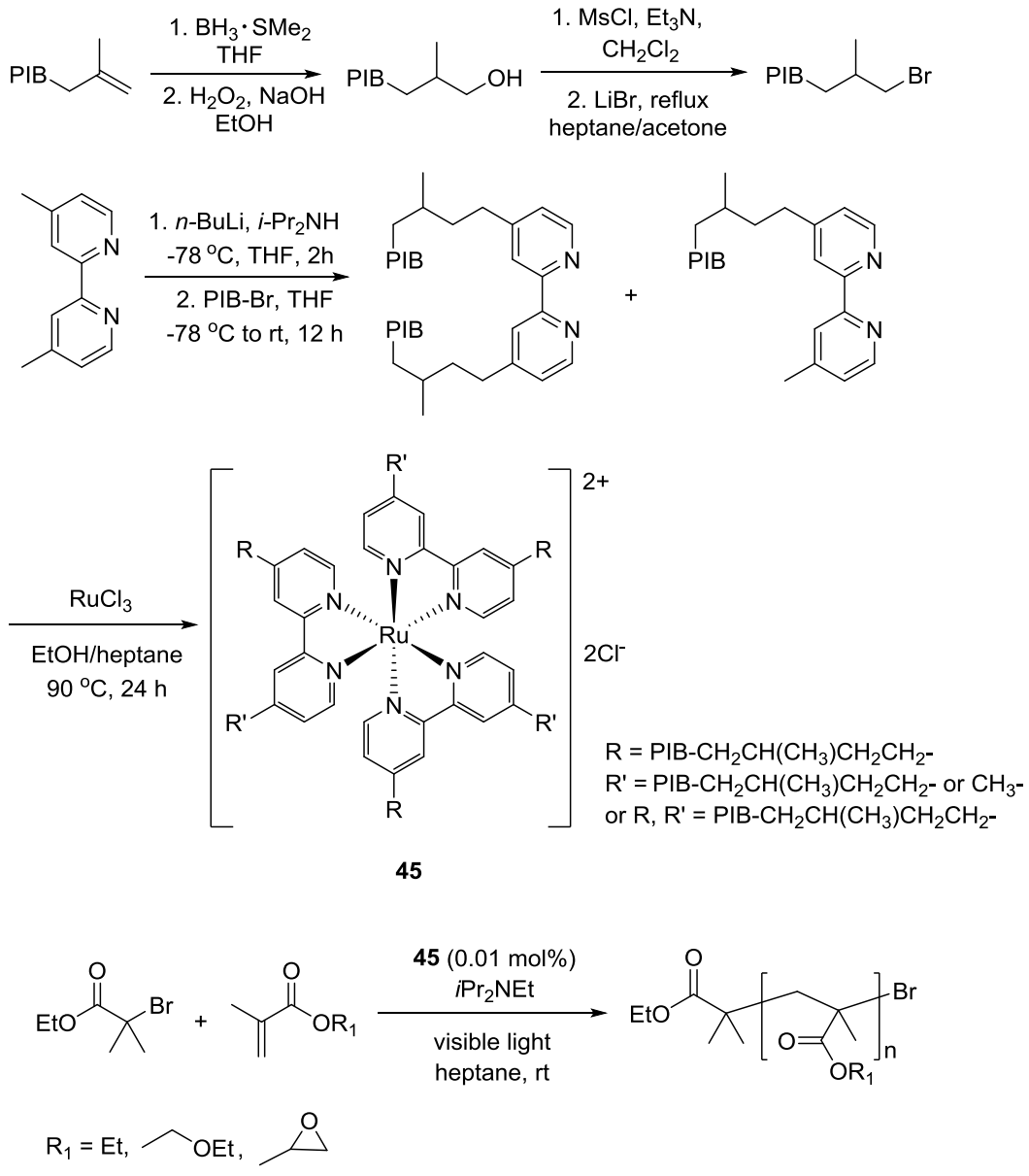
Scheme 31. Visible light-mediated polymerization of methacrylates using ruthenium and iridium photoredox catalysts.

Our interest in this chemistry arose because of our interests in developing effective procedures for reuse of homogeneous catalysts, especially costly and potentially toxic transition-metal catalysts. While such environmental concerns can often be addressed using catalysts immobilized on insoluble supports,[103] catalyst homogeneity

is especially important for photocatalysts like $Ru(bpy)_3Cl_2$ in maximizing the effectiveness of light sources and where flow reactors might be used. Work by various groups including our own has shown that soluble polymer supports serve as useful tools to facilitate recovering catalysts and ligands.[24,104,105]

Given the cost of the Ru catalysts for the above processes and the general desirability of separating catalysts and products, we explored the development of recoverable and reusable photoredox catalysts including PIB-supported Ru(II)-bipyridine complexes photoredox polymerization catalysts.[81] In our initial work, the heptane-soluble PIB-bound Ru(II)-bipyridine [$Ru(PIB\text{-}bpy)_3Cl_2$] complex **45** was prepared using PIB-bound bipyridine ligands formed by alkylation of 4,4′-dimethylbipyridine with PIB-bound bromide. The $Ru(PIB\text{-}bpy)_3Cl_2$ complexes so formed were then used to carry out free radical polymerizations of methacrylates using EB*i*B as the initiator in the presence of *i*Pr_2NEt under visible light irradiation at room temperature (Scheme 32). These soluble polymer-supported catalysts effect polymerizations like their low molecular weight analogs. A facile catalyst/product separation was achieved via a solid/liquid separation, a strategy like one we previously described in styrene polymerization.[53] The polymer products in this case self-separate from the heptane solution of the catalyst when they reach a sufficiently high molecular weight because they precipitated from heptane. The catalyst-containing heptane phase was then recovered and reused with fresh monomer and initiator added. An ICP-MS analysis showed that the isolated polyacrylates contained 1 ppm Ru, a level of Ru

contamination that is about 50-fold less than the Ru leaching in a polymerization catalyzed by the low molecular weight ruthenium catalyst.



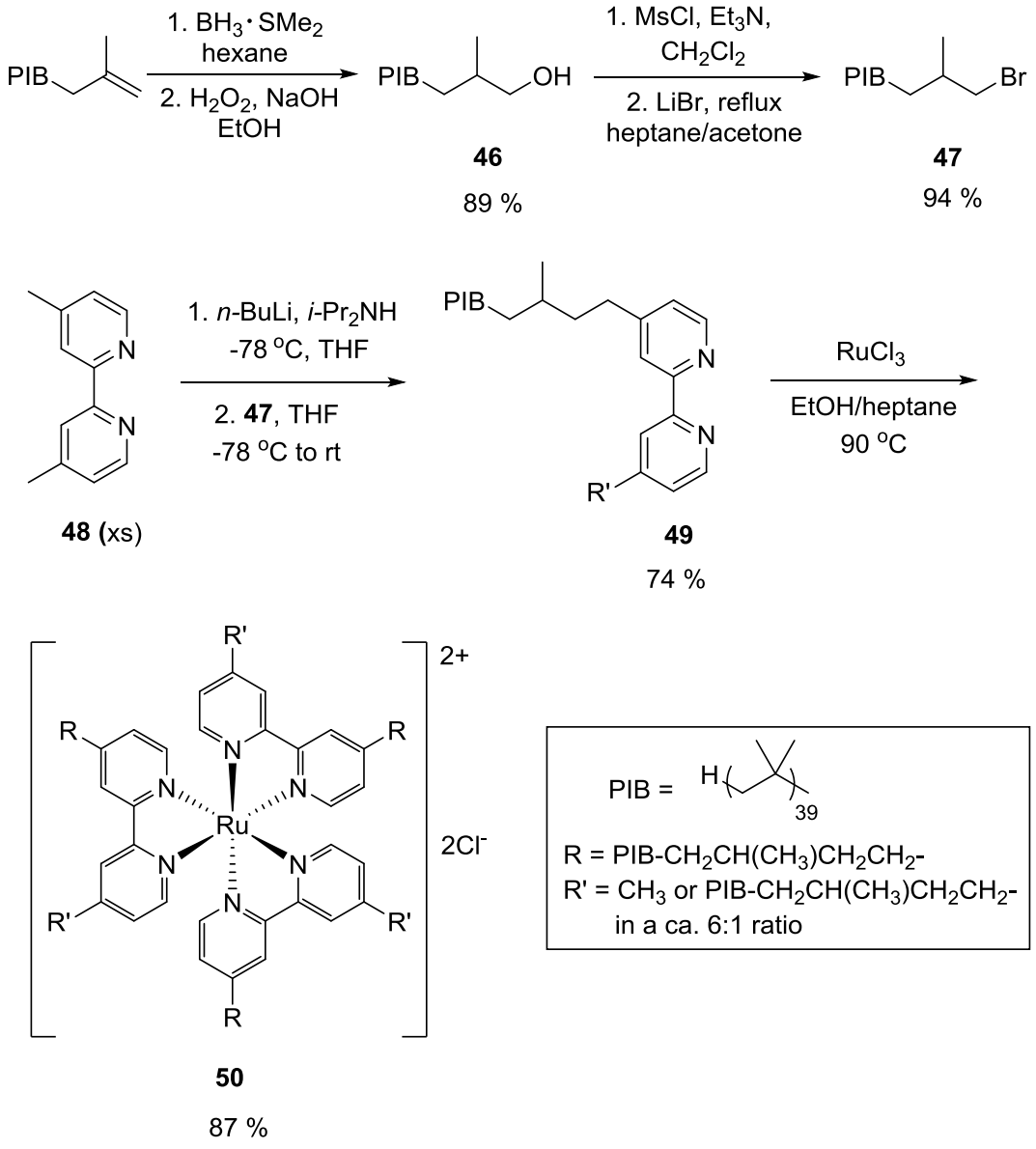
Scheme 32. Visible light-mediated polymerization of methacrylates using PIB-bound Ru(II)-bipyridine complex.

However, since a solid/liquid separation strategy like that described above for an acrylate polymerization is unlikely to be useful in most reactions of this Ru photoredox catalyst where the products and catalysts are both soluble after a reaction or in flow reactors where the formation of solids can be problematic, we wanted to explore the potential of these separable and recyclable $Ru(PIB\text{-}bpy)_3Cl_2$ catalyst in reactions where a liquid/liquid separation of the catalyst could occur. In this work, we explored the broader applicability and limitations of these soluble polymer-supported Ru(II) photoredox catalysts in other known catalytic reactions. The results described below show both the potential and limitations associated with the use of a PIB-supported alkane phase selectively soluble PIB-supported photoredox catalyst in three examples of reactions that are typically effected in moderately polar solvents. Specifically we show how a $[Ru(PIB\text{-}bpy)_3Cl_2]$ catalyst can be used successfully as a recyclable catalyst in an oxidative C-C bond cleavage reaction, less successfully in a [2 + 2] cycloaddition reaction, and unsuccessfully in reactions that convert alcohols to bromides. The principle limitation in these cases is the issue of solvent polarity in that photoredox reactions that require solvents like acetonitrile do not necessarily work as well or at all when solvents compatible with a PIB polymer support are necessary.

Results and Discussion

The preparation of PIB-bound Ru(II)-bipyridine $[Ru(PIB\text{-}bpy)_3Cl_2]$ complexes used here is shown in Scheme 33 and is similar to that that used previously for polymerization catalysts.[81] It began with commercially available alkene terminated PIB

(M_n = 2300 Da), forming an alcohol **46** via a hydroboration/oxidation reaction. This alcohol was then converted first into a mesylate and then into the bromide **47**. In our prior work, we showed that one PIB group per bipyridine is sufficient to produce a phase separable heptane soluble PIB-bound Ru complex. Attempts to convert both methyl groups of a 4,4'-dimethylbipyridine were always incomplete because they were frustrated by some unwanted E2 reactions of **3** with the lithiated bipyridine. Thus, the procedure used for synthesis of photoredox catalysts shown in Scheme 32 was modified. We modified our synthesis by using **47** as the limiting reagent in reaction with the lithium derivative of 4,4'-dimethylbipyridine **48** formed using lithium diisopropylamide (LDA) at -78 °C. This led to a ca. 6:1 mixture of mono- and dialkylated PIB-bound bipyridine ligand **49**. ^{1}H NMR spectroscopic analysis (analyzing the integrals of peak of PIB-$CH_2CH(CH_3)CH_2\underline{CH_2}$- that appeared at 2.74 δ versus the peak of the methyl group at 2.48 δ) was used to show that 15-20% of dialkylated product formed along with **49** even when a stoichiometric excess of **48** was used. The main by-product of this synthesis is unalkylated **48**, which was easily separated from the mixture of PIB-containing products. Other by-products included alkene-terminated PIB that was also separated from **49** by chromatography. We had earlier shown the one PIB group/bipyridyl ligand was sufficient to make **49** or the Ru complex formed from **49** heptane phase selectively soluble. Following our prior procedure, PIB-bound bipyridine ligand **49** was then used to form the PIB-bound Ru(II)-bipyridine complex **50** by allowing PIB-bound bipyridine ligands **49** to react with anhydrous $RuCl_3$ in a heptane/ethanol mixture at 90 °C. The product **50** was isolated as red viscous heptane



Scheme 33. Synthesis of PIB-bound Ru(II)-bipyridine [Ru(PIB-bpy)$_3$Cl$_2$] complex **50**.

soluble oil that was characterized by ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, and UV-visible spectroscopy. Complex **50** had an absorbance at a λ_{max} at 465 nm in hexane that was comparable to the previously reported data of Ru(PIB-bpy)$_3$Cl$_2$ in hexane with

λ_{max} at 463 nm (ε = 15500 M^{-1} cm^{-1}).[81] The Ru complex **50** was as phase selectively soluble in heptane/CH_3CN and heptane/DMF as the other analogs of **50** that were prepared form 100% dialkylated PIB-bound bipyridine or bipyridine ligands containing a 1:2 mixture of mono- and dialklyated bipyridine.

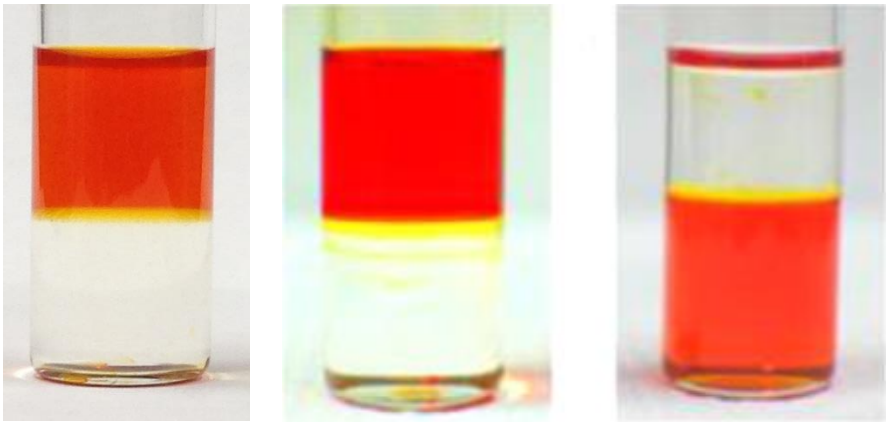
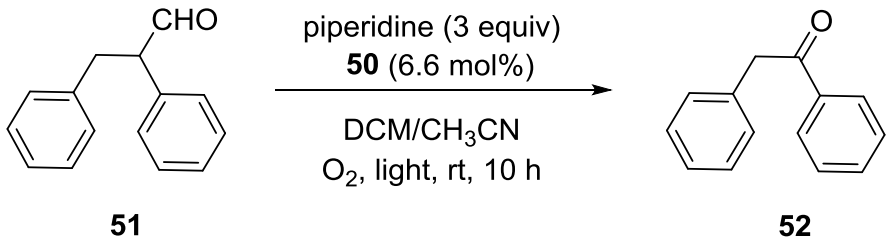


Figure 17. The phase selective solubility of monoalkylated PIB-bound Ru(II) complex **50** (left), dialkylated PIB-bound Ru(II) complex **45** (middle) and the low-molecular weight $Ru(bpy)_3(PF_6)_2$ complex (right) in the heptane/DMF solvent mixture.

Having the PIB-supported ruthenium complex **50** in hand, we first investigated a visible light-mediated oxidative C-C bond cleavage reaction of aldehyde using this complex as a recyclable photoredox catalyst (Scheme 34). This reaction was first explored by Xia and his coworkers[106] using low-molecular weight $Ru(bpy)_3Cl_2$ as the catalyst. In our experiments, reactions were carried out using 2,3-diphenylpropanal **51** with 3 equiv of piperidine in the presence of 6.6 mol% catalyst **50** in a 9/1 (vol/vol) CH_2Cl_2/CH_3CN homogeneous system at ambient temperature using irradiation with a 30

W fluorescent bulb. After irradiation for 10 h, the starting material was fully converted to the desired oxidative C-C bond cleavage product 1,2-diphenylethanone **52**. Reactions were followed by ^{1}H NMR spectroscopy and the reactant aldehyde was fully converted to product (> 98% conversion) after 10 h.



51 **52**

Scheme 34. Oxidative C-C bond cleavage catalyzed by the PIB-bound Ru(II)-bipyridine complex **50**.

As shown in Table 3, the PIB-bound Ru(II)-bipyridine complex **50** showed excellent catalytic activity in this reaction, and can be successfully recovered and reused for 5 cycles with no significant loss of activity. The yield of the product was determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard showed that the yields were essentially quantitative in cycles 1-5. After each cycle, the solvent was removed under reduced pressure. The catalyst was then redissolved in hexane and the product was extracted from the catalyst solution in hexane using CH_3CN. While the crude product was contaminated by excess amine, it could easily be purified by column chromatography. In our experiments, the crude products from all five cycles were combined and further purified by column chromatography. The isolated yield of the

Table 3. Results of oxidative C-C bond cleavage catalyzed by the PIB-bound Ru(II)-bipyridine complex **50**.[a]

Cycle	Yield **52** [%][b][c]
1	99
2	98
3	98
4	99
5	98

[a]Reactions were carried out with 0.25 mmol of aldehyde **51**, 6.6 mol% of **50** and 3 equiv of piperidine at ambient temperature using a 4.5 mL/0.5 mL mixture of CH_2Cl_2/CH_3CN. [b]Yields were determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [c]The product of these five cycles was combined to facilitate isolation of **52**. The yield of product **52** corresponded to an average isolated yield of 96% per cycle.

oxidative C-C cleavage product **52** in this combined material corresponded to 96% yield/cycle. These results are comparable to previously reported results using low-molecular weight $Ru(bpy)_3Cl_2$ photoredox catalyst.[106] Leaching of PIB-supported Ru catalyst into the polar phase during the recycling process was also tested using ICP-MS to measure the Ru contamination in crude product from the third cycle of the reaction. The result of this test showed that the unpurified crude product contained 14 μg Ru which corresponds to ca. 0.9% of the initial amount of Ru used. This leaching was measured after the third cycle so that it measure leaching of catalysts. If the catalyst **50** were only ca. 99% pure, analysis of leaching in cycle 1 would not distinguish between catalyst leaching and an insignificant impurity in the starting catalyst.

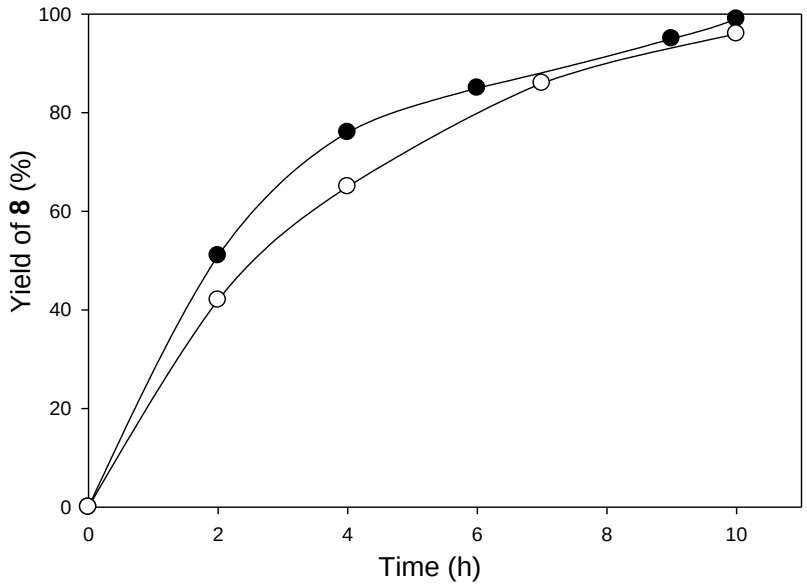


Figure 18. Plot of formation of product **52** versus time in the first cycle of an oxidative C-C cleavage reaction of **51** in either a 9/1 (vol/vol) CH_2Cl_2/CH3CN (●) or a 1/4/1 (vol/vol/vol) heptane/THF/CH_3CN (○) solvent mixture using complex **50** as the catalyst.

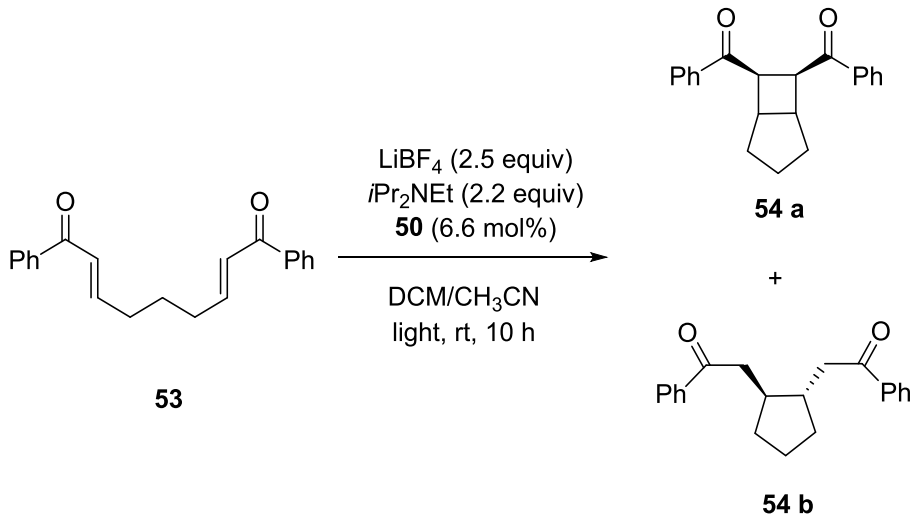
To try to avoid the extraction step in the strategy described above, a second strategy was also briefly studied. In this case, we used a 1/4/1 (vol/vol/vol) heptane/THF/CH_3CN solvent mixture. As can be seen in Figure 18, the first cycle of the reaction was followed by ^{1}H NMR spectroscopy, and the starting aldehyde **51** was fully converted to the desired product **52** after 10 h using visible light irradiation from a 30 W fluorescent bulb at room temperature at essentially the same rate as in the CH_2Cl_2/CH_3CN solvent mixture. The presence of a significantly amount of heptane had no significant effect on the rate of the reaction with a similar yield at 10 h. There was a minor difference in activity with these solvent mixtures, but the differences were not

judged to be significant. This result was also not considered to be significantly different from the 94% yield of this product in 7 h reported previously using a low molecular weight catalyst in CH_3CN.

The heptane/THF/CH_3CN solvent mixture was examined because the PIB-bound Ru(II)-bipyridine complex can be easily recovered via a latent biphasic method using this solvent system by simply adding a 2 mL of water to the 6 mL reaction solution. This addition of water after the reaction causes this latent biphasic solvent mixture to separate into two phases producing an easily isolable less dense heptane-rich catalyst-containing phase that can be directly reused with fresh substrate added for at least 4 cycles. However, while some product can be collected from the denser polar phase, the product **52** has only modest solubility in the water-containing polar phase. Thus, a good yield of **52** using this solvent system was only obtained by combining all portions of the reaction mixture at the end of the catalytic cycles. At this point, the catalyst could be separated from the product by solvent removal and extraction process (*vide supra*) or solvent could be removed from the combined phases and the product could be isolated by column chromatography. In either case, the average isolated yield of 4 cycles of 93% per cycle for the oxidative C-C cleavage product **52** was essentially unchanged from reactions using a CH_2Cl_2/CH_3CN solvent mixture.

With success in an oxidative C-C bond cleavage using this recyclable PIB-bound Ru(II)-bipyridine complex, we next sought to apply this catalyst containing a ca. 6:1 mixture of bipyridyl ligands with one or two PIB groups to other reactions. As I described above, Yoon and his coworkers have demonstrated the work of [2 + 2]

cycloaddition of bis(enone)s using $Ru(bpy)_3Cl_2$ under visible light in CH_3CN as a solvent.[94] This polar solvent is not suitable for **50** as PIB is completely insoluble in CH_3CN.[51] To use the PIB-bound Ru(II)-bipyridine complex **50** as a photoredox catalyst for [2 + 2] cycloaddition of bis(enone) **53** under homogeneous conditions, we used a 4.5 mL/0.5 mL mixture of CH_2Cl_2/CH_3CN to dissolve 6.6 mol% of **50**, bis(enone) **53**, 2.5 equiv of $LiBF_4$, and 2.2 equiv of iPr$_2$NEt. The reaction mixture was then allowed to react at ambient temperature for 10 h using visible light irradiation from a 30 W fluorescent bulb in either CH_2Cl_2/CH_3CN (Scheme 35). As shown in Figure 19, the first cycle of the reaction was followed by ^{1}H NMR spectroscopy, and the conversion of reactant bis(enone) **53** was over 97% after 10 h.



Scheme 35. [2 + 2] cycloaddition of bis(enone) catalyzed by the PIB-bound Ru(II)-bipyridine complex **50**.

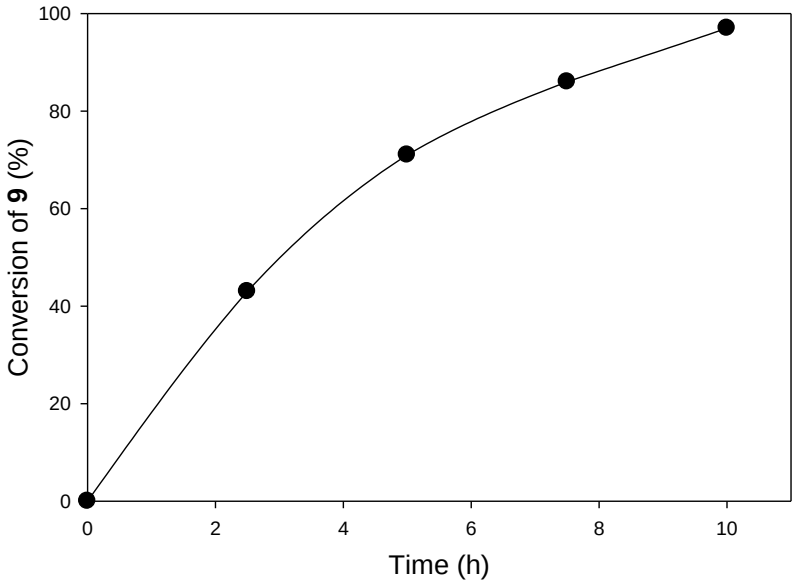


Figure 19. Plot of conversion of bis(enone) **53** vs. time in the first cycle of [2 + 2] cycloaddition in a 9/1 (vol/vol) mixture of CH_2Cl_2/CH_3CN using complex **50** as the catalyst.

As can be seen in Table 4, the PIB-bound Ru(II)-bipyridine complex **50** showed good catalytic activity in this reaction, and the catalyst can be successfully recovered and reused for 5 cycles with no significant loss of activity. In this case, the product isolation, catalyst separation and catalyst recycling procedure followed the procedure described above for conversion of **51** to **52** in this same solvent mixture. However, while **50** could be recycled in this reaction and while the conversion of starting material to products was high, the selectivity for formation of the desired cycloaddition product **54a** was modest under these solvent conditions. A significant amount of the reductive cyclization product **54b** also formed as a side product in the reaction. When the crude

products of these five cycles were combined, we were able to separate these two compounds by column chromatography. The average isolated yield of the cycloaddition product **54a** was 210% (42%/cycle) and the reductive cyclization product **54b** was 195% (39%/cycle). ^{1}H NMR spectroscopic analysis of the crude product in cycles 1 and 2 showed that **54a** and **54b** were present in a roughly 1/1 ratio. The conversion in cycle 4 was anomalously lower than that in cycle 3 or 5. We did not further investigate this discrepancy. The crude product from the third cycle of the reaction was analyzed by ICP-MS to measure the Ru contamination, and the result showed that 1.1% of catalyst **50** (18.6 μg Ru) leached into the acetonitrile phase.

Table 4. Results of [2 + 2] cycloaddition of bis(enone) catalyzed by the PIB-bound Ru(II)-bipyridine complex **50**.[a]

Cycle	Yield of **54a** and **54b** [%][b]	Yield **54b** [%][b][c][d]
1	98	51
2	99	41
3	94	39
4	65	29
5	98	60

[a]Reactions were carried out with 0.25 mmol of bis(enone) **53**, 6.6 mol% of **50**, 2.5 equiv of $LiBF_4$, and 2.2 equiv of *i*Pr_2NEt at ambient temperature using a 4.5 mL/0.5 mL mixture of CH_2Cl_2/CH_3CN. [b]Yields were determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [c]The average isolated yield of product **54a** for 5 cycles is 42%/cycle. [d]The average isolated yield of product **54b** for 5 cycles is 39% per cycle.

While the yield of the recovered catalyst **50** was not directly measured quantitatively by a technique like ICP-MS, we did observe that there was no visual leaching of the highly chromogenic catalyst **50** into the product phase. In recycling **50**, we used recovered **50** in the same volume of solvent and observed that a visually identical intensity orange-red solution of **50** was reformed in cycles 2 and 3. This qualitative colorimetric assay suggests that >90% of the catalyst is recovered. We postulated that the formation of a mixture of two products in this reaction is due to the solvent change. Hence, we carried out an experiment using the conventional low molecular weight $Ru(bpy)_3Cl_2$ catalyst for the [2 + 2] cycloaddition of bis(enone) **53** in 4.5 mL/0.5 mL of CH_2Cl_2/CH_3CN under the same conditions used with **54**. While the bis(enone) **53** in this experiment was fully consumed, it again formed a mixture of products **54a** and **54b** after 1 h. In this case, the two products were isolated by column chromatography to yield 31% of product **54a** and 61% of product **54b**.

We also briefly explored other solvents mixtures. We found that the use of an alternative heptane/THF/CH_3CN solvent system for the [2 + 2] cycloaddition was less successful. The conversion of the starting bis(enone) **53** under visible light irradiation was slower and required over 24 h to before it was above 90%. Again, while we were able to separate and reuse **50** for 4 cycles using the latent biphasic strategy, both cycloaddition product **54a** and reductive cyclization product **54b** again formed. In this case, the average isolated yield of the cycloaddition product **54a** was 16%/cycle and the reductive cyclization product **54b** was 60%/cycle.

Scheme 36. Attempted conversion of alcohol to halide by the PIB-bound Ru(II)-bipyridine complex **50**.

The solubility limitations of **50** that required the presence of a less polar solvent and that led to a mixture of products in the [2 + 2] chemistry were even more problematic in attempts to use **50** to convert alcohols to bromides (Scheme 36).[107] In this case, we were able to use a low molecular weight catalyst $Ru(bpy)_3Cl_2$ in DMF to form 1-bromo-3-phenylpropane **56** (Scheme 36). However, when this same reaction was carried out using 3-phenyl-1-propanol **55** with 2 equiv of CBr_4, and 2 equiv of NaBr in the presence of 1.3 mol% catalyst **50** in a 4/1 (vol/vol) mixture of CH_2Cl_2 and DMF at ambient temperature for 20 h under irradiation of blue LED no bromide formed. Based on our experience with the [2 + 2] cycloadditions, we thought that the solvent change could be the cause of failure for this reaction. A control experiment using $Ru(bpy)_3Cl_2$ as a catalyst to carry out this reaction in the same 4/1 (vol/vol) mixture of CH_2Cl_2/DMF also produced no product, suggesting that the lack of solubility of **50** in polar solvents would preclude its use in this chemistry.

Conclusions

In conclusion, a PIB-bound Ru(II)-bipyridine complex was prepared, and we demonstrated that this PIB-supported Ru complex can be used as a recyclable photoredox catalyst to carry out oxidative C-C bond cleavage of aldehyde in CH_2Cl_2/CH_3CN homogeneous system efficiently. In addition, a visible-light induced [2 + 2] cycloaddition of bis(enone) can also occur with high conversions of the bis(enone) using this PIB-bound Ru(II)-bipyridine complex. However, using solvents that dissolve the PIB catalyst lead to the formation of both cycloaddition and cyclization products. In a third case, the substitution of solvents other that CH_3CN was completely unsuccessful. The results indicated that this PIB-supported Ru catalyst can be successfully recycled and reused for at least 5 cycles though successful use of this soluble catalyst requires a solvent tolerant reaction. This illustrates a general limitation of these PIB supported catalysts (and other phase selectively soluble polymer supported catalysts) in that the different solvent systems needed for a specific support can lead to longer reaction times, altered selectivity, or in the case of the alcohol to halide reaction, no reaction at all. These PIB-supported catalysts and a biphasic liquid/liquid separation based catalyst recycling strategy can be applied to other photoredox reactions if the reaction tolerates less polar solvent. If this type of catalyst recycling were to be effective in photoredox [2 + 2] cycloadditions or in alcohol to halide reactions, a polar solvent soluble polymer support would be required so that a more polar medium could be used for the photoredox catalysis chemistry.

CHAPTER IV

RECYCLABLE POLYISOBUTYLENE (PIB)-BOUND ORGANIC PHOTOREDOX CATALYST CATALYZED POLYMERIZATION REACTIONS*

Introduction

Recent advances in new ways to effect controlled living polymerizations using atom transfer radical polymerization (ATRP), nitroxide-mediated radical polymerization (NMP), reversible addition-fragmentation chain transfer (RAFT), ring opening metathesis polymerization (ROMP), and acyclic diene metathesis (ADMET) chemistry have provided ways to prepare polymers with well-defined structures and properties.[108-117] Photocatalysis that uses visible light to effect reactions is an alternative type of catalysis and a variety of photoredox catalysts have been used for a broad range of synthetic transformations including polymerization chemistry.[84,85,118,119] However, while transition-metal photoredox catalysts show excellent catalytic activity and selectivity in these reactions, the metal contamination in products could be problematic for biomedical or electronic applications. Recent work from a number of groups has suggested that organic photoredox catalysts are useful tools not only for the synthesis of low molecular weight compounds but are also effective in controlled polymerization reactions including ATRP, ROMP, and living cationic polymerizations and prepared the polymers

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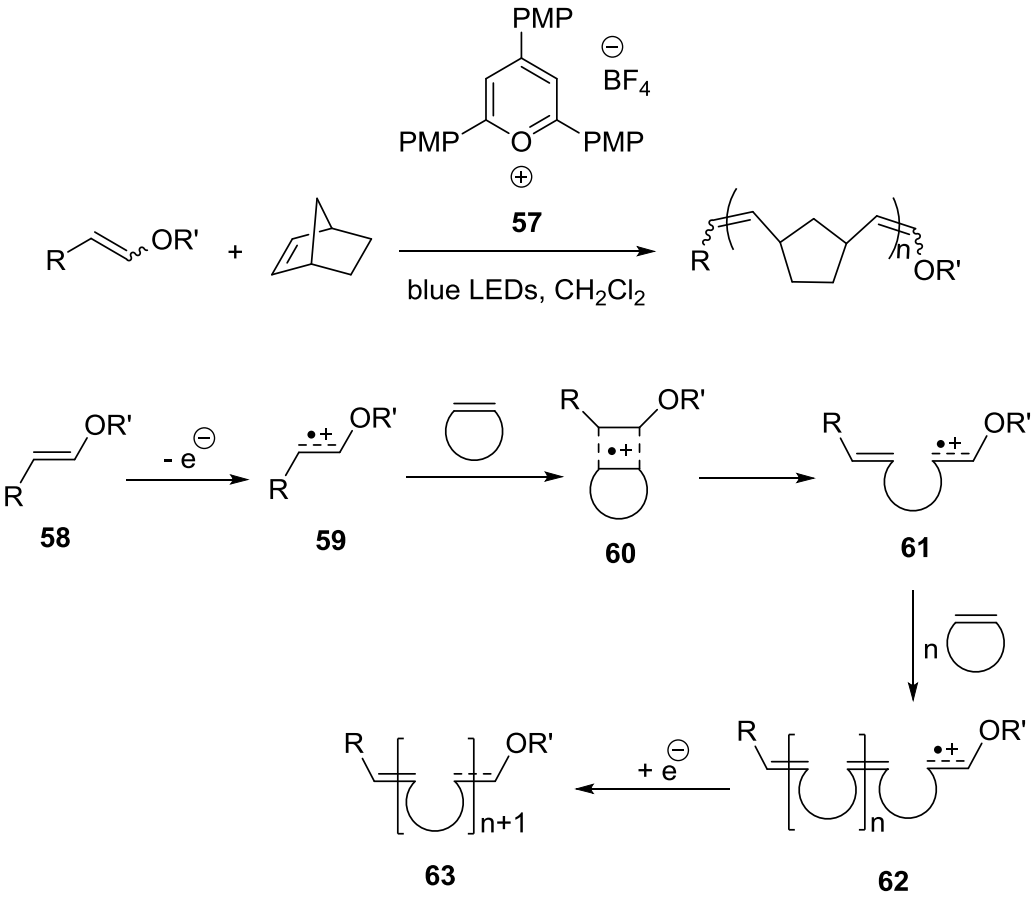
* Reprinted with permission from "Recyclable Polyisobutylene (PIB)-bound Organic Photoredox Catalyst Catalyzed Polymerization Reactions" by Liang, Y.; Bergbreiter, D. E. *Polym. Chem.* **2016**, *7*, 2161-2165.

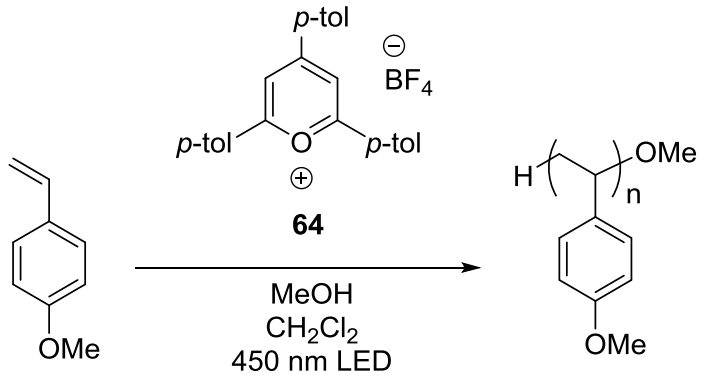
without metal contamination.[120-126] Upon exposure to light, these organocatalysts effect polymerizations through the reductive or oxidative quenching pathways similar to the transition-metal photoredox catalysts.



Scheme 37. Light-mediated ROMP using pyrylium salt photoredox catalyst.

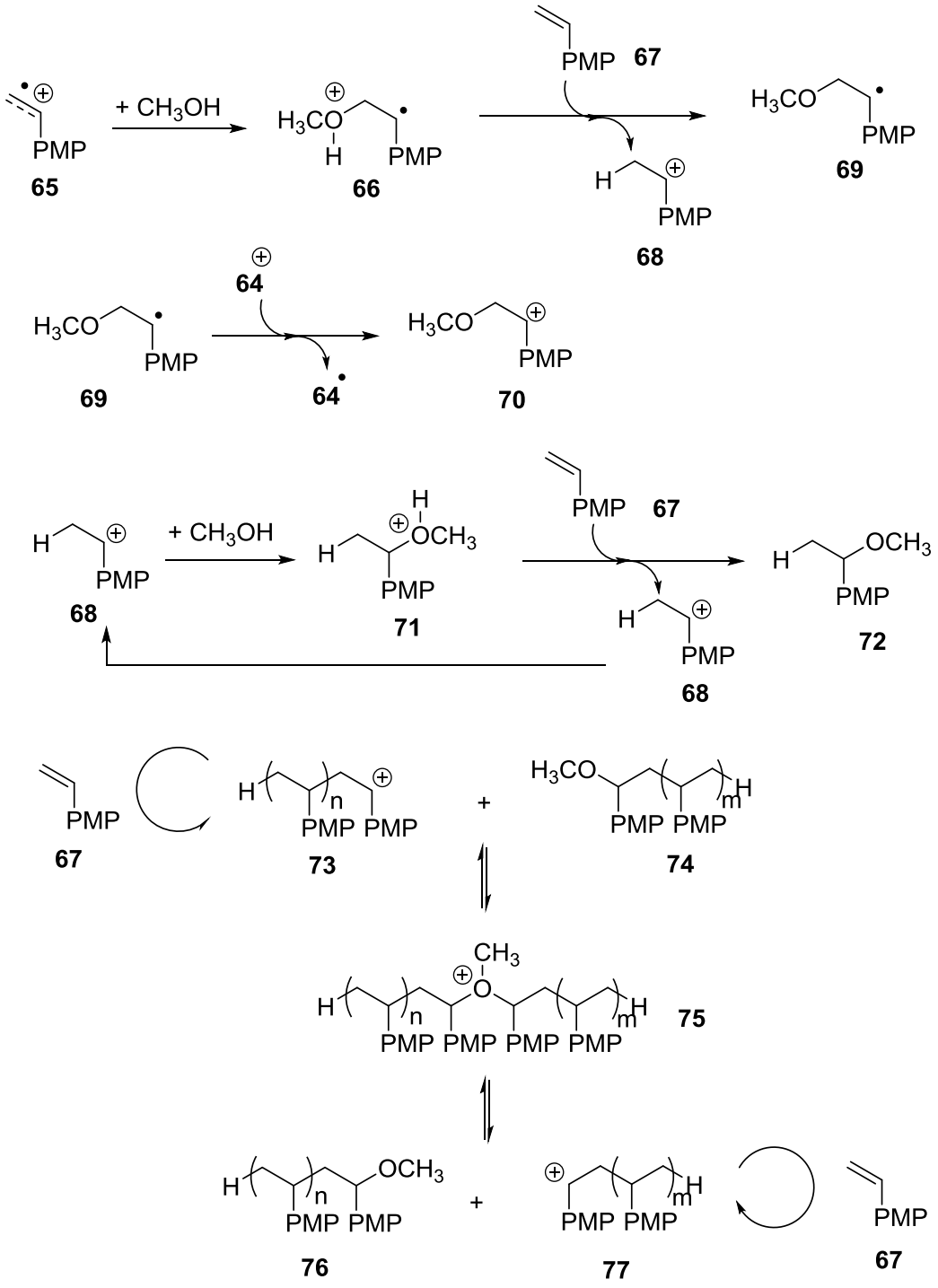
Boyston and coworkers developed the first example of a metal-free ROMP process using an organo photoredox catalyst (Scheme 37).[123] In this case, the reaction was carried out using the norbornene, vinyl ether initiator in the presence of the 2,4,6-tri-

(*p*-methoxyphenyl) pyrylium tetrafluoroborate **57** in CH_2Cl_2 under irradiation of blue LEDs. High conversions of monomer and linear relationship between molecular weight and conversions were observed. The polymerization is initiated by oxidation of the vinyl ether initiator **58** via electron transfer to the excited pyrylium species and generates an activated radical cation **59**. The vinyl ether radical cation reacts with the monomer to form a complex **60**, and the ring opening of **60** generates **61**. Propagation of **61** with additional monomers produces polymer **62** with a radical cation chain end. Reduction of the radical cation chain end can lead to the formation of the polymer **63**.



Scheme 38. Light-mediated cationic polymerization using pyrylium salt catalyst.

Nicewicz *et al.* described an example of visible light-induced living cationic polymerization utilizing 2,4,6-tri(*p*-tolyl) pyrylium tetrafluoroborate salt (Scheme 38).[124] The cationic polymerization of 4-methoxystyrene was conducted using **64** in the presence of methanol in CH_2Cl_2 using blue LEDs. Under this condition, poly(4-methoxystyrene) was obtained in high yield with low dispersity. Moreover, the study

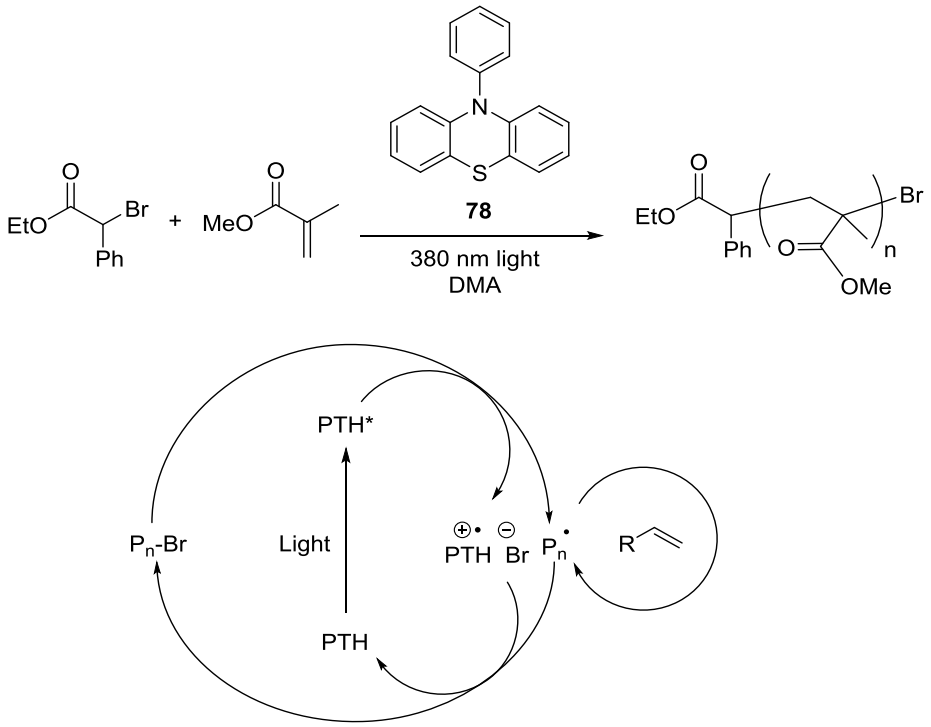


Scheme 39. Mechanism of light-mediated living cationic polymerization.

indicated that the methanol concentration can effect the molecular weight and molecular weight distribution of the polymer. As shown in Scheme 39, photoexcitation of the organocatalyst initiates the process and generates a cation radical **65**. The addition of methanol to **65** produces the methanol captured cationic radical **66** that can protonate a monomer to afford **68** with an active cationic chain end. The resulting radical **69** is then oxidized by the catalyst to form a cation **70**. The cation **68** is captured by methanol and affords **71** that can protonate a monomer to form an active cationic chain end, and this process is repeated until all methanol is consumed. The polymerization is controlled via a reversible chain transfer process, the cationic chain end of **73** is captured by the methoxy group of **74** to produce an oxonium ion intermediate **75**, which can fragment into a dormant methoxy group terminated chain **76** and an active cationic chain **77**. The active chain undergoes propagation until a new oxonium ion intermediate is generated.

Hawker and coworkers demonstrated that they could effect a metal-free ATRP process using methacrylate as a monomer using 10-phenylphenothiazine (PTH) **78** as an organic photocatalyst (Scheme 40).[125] In this chemistry, visible light irradiation of PTH produces the excited PTH^{*} that reduces the alkyl halide initiator to generate the alkyl radical that reacts with the monomer. The $PTZ^{+\bullet}Br^{-}$ complex then deactivates the propagating chain to generate the polymer with a bromine end group and the ground state PTH. The regenerated PTH can repeat this catalytic process. This strategy can generate polymer products with excellent control over molecular weight and low molecular weight distribution that are comparable to results that can be achieved using a conventional Cu-catalyzed ATRP or a Ru or Ir photoredox mediated ATRP process. The

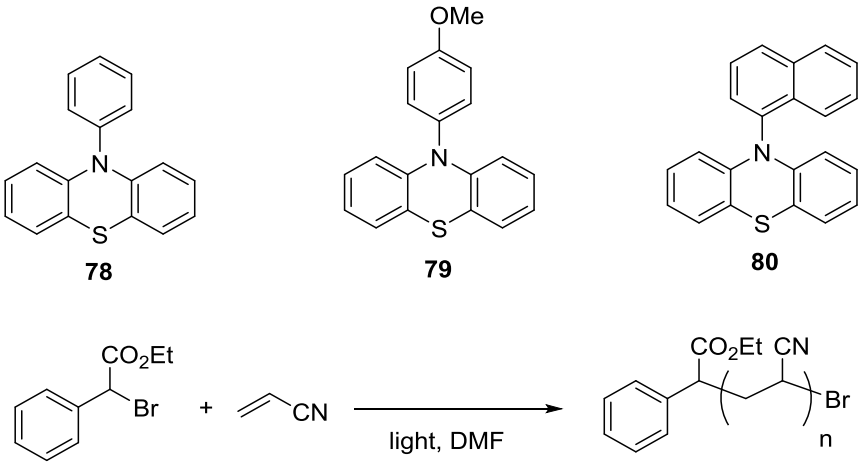
reaction was also monitored using **78** under light on and light off conditions, and the results showed that the polymerization process is strictly controlled with light.



Scheme 40. Light-mediated ATRP of methacrylate using 10-phenylphenothiazine.

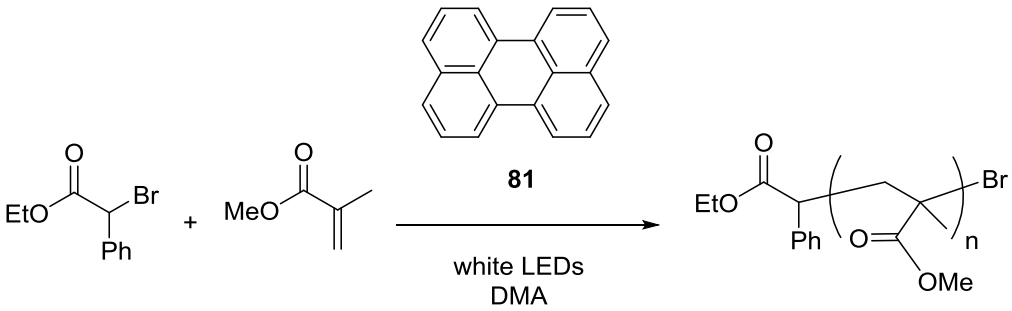
Matyjaszewski group reported another example of a light-induced ATRP process using acrylonitrile as a monomer with phenothiazine derivatives as organo photoredox catalysts (Scheme 41).[126] The metal-free ATRP reaction was performed using acrylonitrile, 10-phenylphenothiazine, and ethyl α-bromophenylacetate (EBPA) in DMF under UV light irradiation. Phenothiazine derivatives **79** and **80** were also investigated and produced the polyacrylonitrile under similar conditions. In addition, ATRP of acrylonitrile using a stronger UV light source was examined, and higher conversion of

the monomer and better control of the polymer were observed. The chain extension polymerization of polyacrylonitrile with methyl methacrylate was performed, and the formation of the block copolymer indicated that polyacrylonitrile had bromine chain-end functionality.



Scheme 41. Light-mediated ATRP of acrylonitrile using phenothiazine catalysts.

Theriot *et al.* also developed a metal-free ATRP process using a perylene photoredox catalyst (Scheme 42).[120] In this case, the polymerization of methyl methacrylate was carried out using catalyst **81**, initiator in DMF using irradiation by white LEDs. The polymer was formed in modest yield with narrow PDI. In addition, the results showed that the polymerization proceeded in the presence of light and no reaction occurred in the dark. Together, these various studies demonstrated that light-mediated polymerization processes using organo photoredox catalysts can provide environmental metal-free pathways for polymer synthesis.



Scheme 42. Light-mediated ATRP of methacrylate using perylene oranocatalyst.

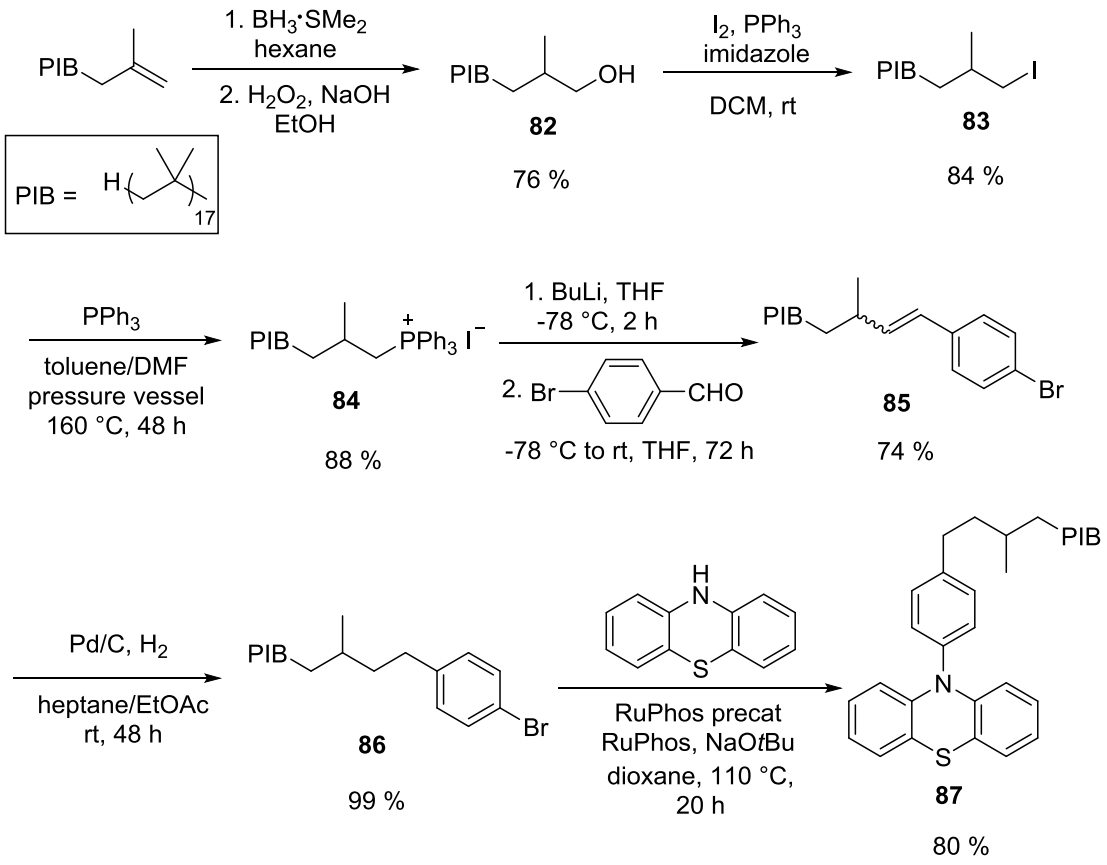
Our group has a history of developing effective strategies for recovery and reuse of catalysts.[10] This work has also used soluble polymer supports that effect separation and recycling of catalysts in polymerizations. Issues including catalyst cost, catalyst toxicity, or just the undesired presence of catalyst contamination like product discoloration that might affect a polymer product's properties or uses makes catalyst recycling desirable.[43,53,81,127-129] An example of this prior work in the case of photocatalysis is our development of a PIB-bound Ru(II) photoredox catalyst for light-mediated radical polymerizations of acrylates,[81] a catalyst that was also recyclable in oxidative C-C bond cleavage reactions and in [2+2] cycloaddition reactions that were described in the previous chapter (cf. Chapter III).[130]

In the work discussed in this chapter, we show that PIB can serve as a polymer support to recover and reuse a heptane-soluble PIB-bound 10-phenylphenothiazine (PIB-PTH) organo photoredox catalyst. This PIB-bound organocatalyst is effective in the light-mediated radical polymerization reactions of acrylate monomers, has good catalytic

activity and recyclability, and provides modest control over the polymer molecular weight and polydispersity.

Results and Discussion

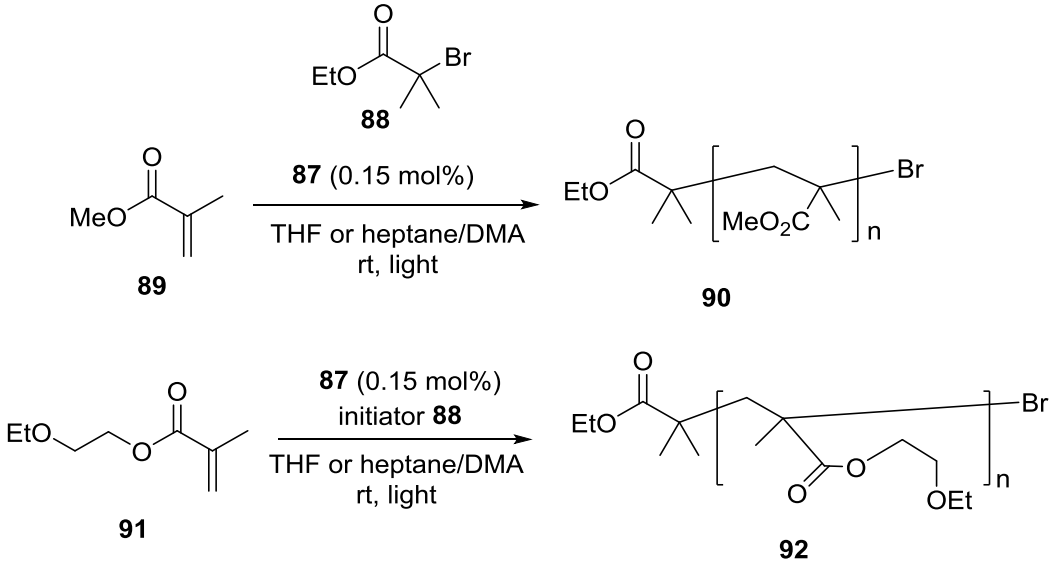
The synthesis of this PIB-bound 10-phenylphenothiazine (PIB-PTH) photoredox catalyst is shown in Scheme 43. Commercially available alkene terminated PIB (M_n = 1000 Da) was first converted to a PIB-bound alcohol **82** which was then allowed to react with iodine in the presence of triphenylphosphine and imidazole to generate the PIB-bound iodide **83**. This iodide **83** was used to form the triphenylphosphonium salt **84** by allowing **83** to react with triphenylphosphine in a pressure vessel. We then used a Wittig reaction followed by a Pd/C-catalyzed hydrogenation, to form the PIB-bound bromobenzene ligand **86**. This PIB-bound bromobenzene **86** was then coupled with phenothiazine to form the desired PIB-bound phenothiazine (PIB-PTH) catalyst **87** by a Pd-catalyzed C-N coupling reaction. The product that was isolated by column chromatography was characterized by ^{1}H and ^{13}C NMR spectroscopy. A synthesis of **87** using a CF_3SO_3H-catalyzed electrophilic aromatic substitution reaction of PIB in neat bromobenzene was also briefly examined. However, this reaction was unsuccessful at 25 °C. Attempts to carry out this electrophilic aromatic substitution at elevated temperature were not explored since other studies showed that polyisobutylene depolymerization occurs in acid-catalyzed electrophilic substitutions of deactivated arenes at higher temperatures.[52]



Scheme 43. Synthesis of the PIB-bound PTH organic photoredox catalyst **87**.

We first investigated the visible light-mediated radical polymerization of acrylates using this PIB-bound organocatalyst **87** as a recyclable photoredox catalyst using methyl methacrylate **89** as the monomer, carrying out reactions using 0.15 mol% of the PIB-bound PTH catalyst **87** and 30 μL of the initiator ethyl 2-bromoisobutyrate **88** in 3 mL of heptane under the irradiation of a 23 W fluorescent bulb at ambient temperature for 20 h. This approach was based on our prior work with Ru photoredox catalysts. However, while poly(methyl methacrylate) (PMMA) formed in modest yield and the solid product polymer precipitated out from the heptane solution of the **87** during

the reaction, this procedure produced product **90** with a relatively high polydispersity index (PDI) (entry 1, Table 5). Therefore, we sought to conduct the reaction under homogeneous conditions to get a better control over the polymerization process. This was accomplished by using THF as a solvent (Scheme 44). In this case, a homogeneous reaction did occur. As shown in entries 2-4 of Table 5, the catalyst could be recycled and **90** was isolated in good yield at modest conversion.



Scheme 44. Light-mediated radical polymerizations of alkyl acrylates catalyzed by the PIB-bound PTH organo photoredox catalyst **87**.

In a typical procedure, 15 μmol of **87** and 1 mL of methyl methacrylate was dissolved in 2 mL of THF. After 3 freeze-pump-thaw degassing cycles, 0.24 mmol of **88** was injected via syringe. Then the reaction mixture was allowed to stir under the irradiation of a 23 W household fluorescent bulb at ambient temperature for 15 h at

which point the THF was removed at reduced pressure and the catalyst was removed from the residue using 4 mL of heptane. The crude polymer was dissolved in 0.3 ml of THF and precipitated using 10 mL of heptane and the product isolated by filtration. The catalyst containing heptane solution was then concentrated under reduced pressure using a rotary evaporator. The recovered catalyst was reused for the following cycle by adding fresh monomer, initiator, and THF as shown in Figure 20.

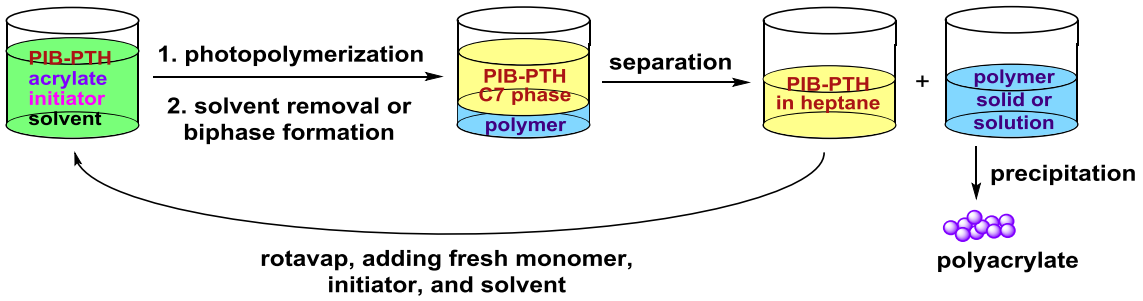


Figure 20. General scheme for polymer product/catalyst separation and recycling of PIB-bound PTH catalyst **87**.

For comparison purposes, we examined a polymerization of **89** using the low molecular weight *N*-phenylphenothiazine photocatalyst **78**.[125] This experiment was carried out in THF under the same conditions used in a polymerization of **89** with PIB-PTH **87**. The results of a 22% conversion and an 82% isolated yield of PMMA that had an M_n of 2.4 kDa and a PDI of 1.38 are very comparable to the results in Table 5 seen using the PIB-bound catalyst **87**.

We also examined solvent mixtures as a medium for the polymerization. We had hypothesized that adding some *N*,*N*-dimethylacetamide (DMA) to heptane would keep the growing polymer in solution and afford better control of the polymerization and a more efficient biphasic separation of product and catalyst. In the event, we found out that polymerization in a 1.75 mL/0.25 mL mixture of heptane/DMA under the same conditions used with THF led to similar control of the molecular weight distribution of the product as seen in THF with comparable isolated yields of the product poly(methyl methacrylate) **90**. Using this scheme, the PIB-supported organocatalyst **87** was also recovered and reused for 3 cycles with no significant loss of activity. In the recycling experiments, additional DMA was first added to the reaction mixture to insure that all the polymer was in solution when the two phases were separated. Then the phases were separated. The product was isolated from the DMA phase by precipitation using a large excess of heptane. The catalyst was separately recovered from the heptane phase by removing solvent and residual monomer under reduced pressure. The recovered catalyst was then reused using fresh heptane, DMA, fresh monomer and initiator (Figure 20). The isolated yield of the polymer **90** was 90%, 100%, and 94% in cycles 1-3. The isolated polymer **90** from each cycle was analyzed by gel permeation chromatography (GPC). The results showed that the M_n of the polymer was 3.1 kDa to 3.4 kDa with a PDI that varied from 1.27 to 1.41, numbers that are similar to those seen in THF (Table 5).

Table 5. Light-mediated radical polymerizations of methacrylates using the PIB-bound PTH organocatalyst **87**.

Entry	Monomer	Cycle	Conversion [%][a]	Yield [%][b]	M_n [kDa][c]	PDI[c]
1[d]	**89**	-	-	34	39.1	3.71
2[e]	**89**	1	23	84	2.4	1.33
3[e]	**89**	2	26	86	2.8	1.39
4[e]	**89**	3	25	81	2.6	1.42
5[f]	**89**	1	21	90	3.3	1.32
6[f]	**89**	2	20	100	3.1	1.41
7[f]	**89**	3	18	94	3.4	1.27
8[g]	**91**	1	70	98	13.7	1.67
9[g]	**91**	2	75	99	14.4	1.70
10[g]	**91**	3	57	94	12.6	1.63
11[h]	**91**	1	34	89	8.5	1.46
12[h]	**91**	2	31	94	8.1	1.50
13[h]	**91**	3	33	94	9.4	1.78

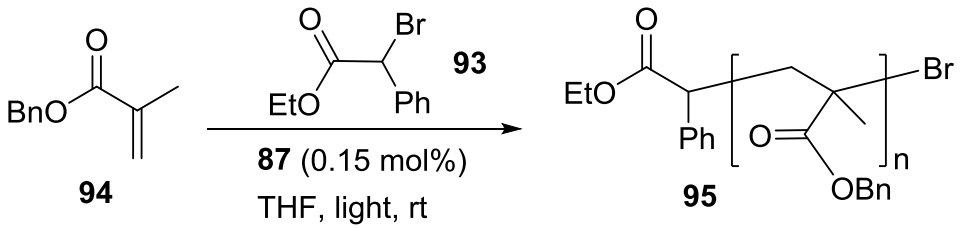
[a]Conversions of the monomer were determined by ^{1}H NMR spectroscopy. [b]Isolated yields of the polymer based on the conversion of the starting monomer. [c]M_n and PDI were determined by gel permeation chromatography. [d]Reaction was carried out using 9.3 mmol of **89**, 0.15 mol% of **87**, and 30 μL of **88** in 3 mL of heptane at RT. [e]Reactions were carried out using 9.3 mmol of **89**, 0.15 mol% of **87**, and 30 μL of **88** in 2 mL mixture of THF at RT. [f]Reactions were carried out using the same amounts of **89**, **87**, and **88** as in THF but in a 1.75 mL/0.25 mL mixture of heptane/DMA at RT. [g]Reactions were carried out using 9.8 mmol of **91**, 0.15 mol% of **87**, and **88** in a 2.1 mL/0.3 mL mixture of heptane/DMA at RT. [h]Reactions were carried out using the same amounts of **91**, **87**, and 30 μL of **88** as in THF but in a 2.0 mL/0.5 mL mixture of 0.5 mL mixture of heptane/DMA at RT.

A polymerization of **91** in a 2.0 mL/0.5 mL mixture of heptane/DMA was also carried out. In this case, more DMA led to a higher conversion of **91** to the polymer **92**. The polymer-supported catalyst **87** was again recovered and reused for 3 cycles with no significant loss of activity (Table 5, entries 8-10), affording polymer **92** in 89%, 94 %, and 94% isolated yield in cycles 1-3. These results and our other results suggest that better control over the polymerization with less variation of the M_n and lower PDI are obtained when **87** is used in more polar solvents or in solvent mixtures containing more polar solvents. The solvent effects noted by the varied PDI values in Table 5 are consistent with prior observations that photoredox catalyst chemistry with PIB-bound photoredox catalysts that is carried out in moderately polar solvents can be effected by the presence of heptane.[23]

We showed that this strategy was also effective with other monomers. In this case, 2-ethoxyethyl methacrylate **91**, 0.15 mol% of the catalyst **87**, and 30 μL of ethyl 2-bromoisobutyrate in a 2.1 mL/0.3 mL mixture of heptane/DMA under the irradiation of a 23 W CFL bulb at ambient temperature. As expected, **91** was converted to the desired product **92**, poly(2-ethoxyethyl methacrylate), after 15 h (Table 5). The PIB-supported organocatalyst **87** was recovered and reused for 3 cycles with slightly lower conversion in the third cycle. The catalyst showed modest control over the molecular weight distribution of the polymer product and high conversions of the monomer in this reaction. The average isolated yields of three cycles of polymer **92** were all above 95%. After each cycle, the catalyst separation and recycling process followed the procedure described above. The isolated polymer from each cycle was analyzed by GPC. The

results showed that the M_n of the polymer was between 12.6 kDa to 14.4 kDa with a PDI that varied from 1.63 to 1.70.

A series of kinetic studies of this PIB-PTH catalyzed radical polymerization process were also performed with a different monomer. These studies used benzyl methacrylate **94**, 0.15 mol% of the catalyst **87**, 30 μL of the ethyl 2-bromoisobutyrate irradiation from a 23 W CFL bulb at room temperature, and were carried out in a homogeneous system using 2 mL of THF.



Scheme 45. Light-mediated radical polymerization of benzyl methacrylate using the PIB-bound PTH catalyst **87**.

The first of these studies examined the polymerization of **94** under both light-on and light-off conditions. The experiment was carried out in the presence of the benzyl methacrylate **94**, and the reaction was monitored by ^{1}H NMR spectroscopy. As shown in Figure 21, the expected result was observed, and the plot showed that there was no consumption of the monomer during the light-off period, and that the monomers were gradually consumed to form polymer when the reaction mixture was exposed to light. These results that show a polymerization process that occurs with light irradiation and

stops in the dark are comparable to results seen with low molecular weight PTH photoredox catalysts.

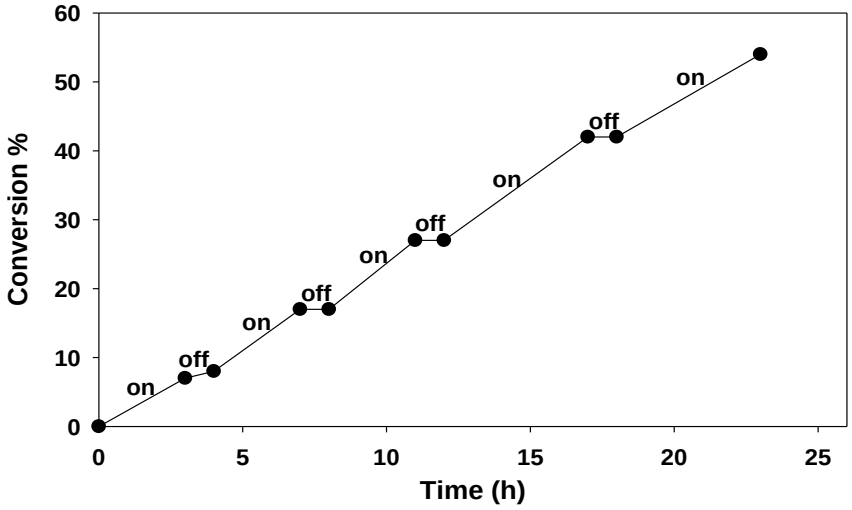


Figure 21. Polymerization of monomer **94** in the presence or absence of light using PIB-bound PTH catalyst **87**.

Additionally, we performed a kinetic study by carrying out the polymerization in the presence of the monomer **94**, 0.15 mol% of the catalyst **87**, 35 μL of a more reactive initiator **93**, ethyl 2-bromophenylacetate, in 2 mL of THF under the irradiation of a 23 W CFL bulb at room temperature (Scheme 45). The conversions of benzyl methacrylate were monitored by taking aliquots of the reaction mixture at different times and analyzed by ^{1}H NMR spectroscopy. The M_n and the PDI of the poly(benzyl methacrylate) (PBnMA) were also determined by GPC. GPC traces for polymers formed using **87** are similar at different conversions (Figure 22).

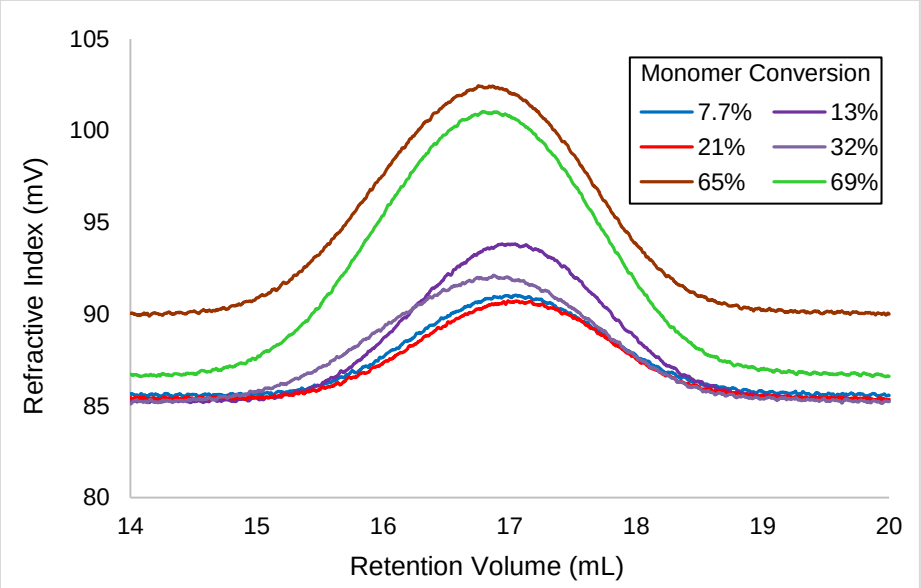


Figure 22. GPC trace of PBnMA **95** at different conversions.

Plots of the conversion (Figure 23) and the $\ln([M]_0/[M]_t)$ (Figure 24) versus time of light exposure showed that the polymerization proceeded slowly at the beginning of the reaction. After this initial period, the conversion of the monomer increased and a more linear semi-logarithmic plot was observed that suggested a first-order reaction. However, as shown in Figure 25, the nonlinear growth of the molecular weight versus conversion and the M_w/M_n values over 1.4 is consistent with a less controlled polymerization process that could be due to a less efficient initiation process or a slow deactivation step, issues that could account for the higher PDI and the molecular weights that are higher than would be expected for a controlled polymerization.

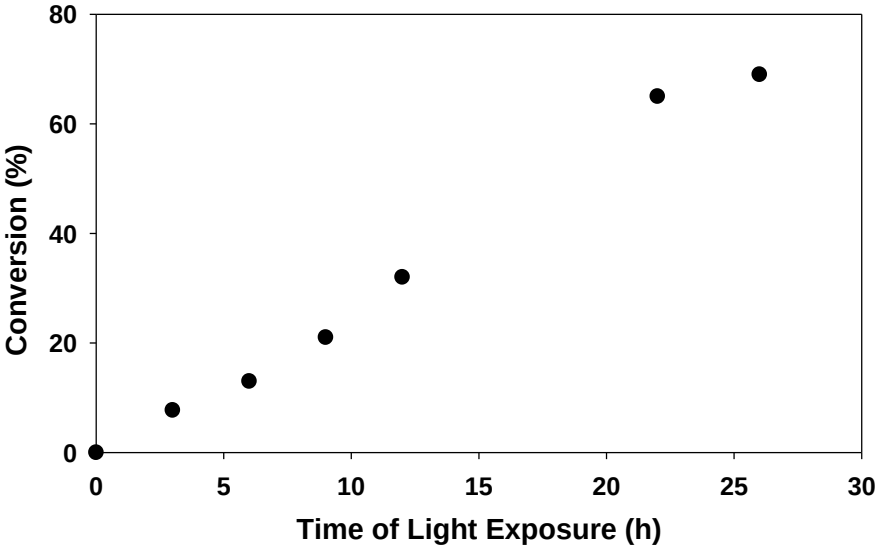


Figure 23. Plot of conversion of monomer **94** versus time of radical polymerization using PIB-bound PTH **87** as a catalyst.

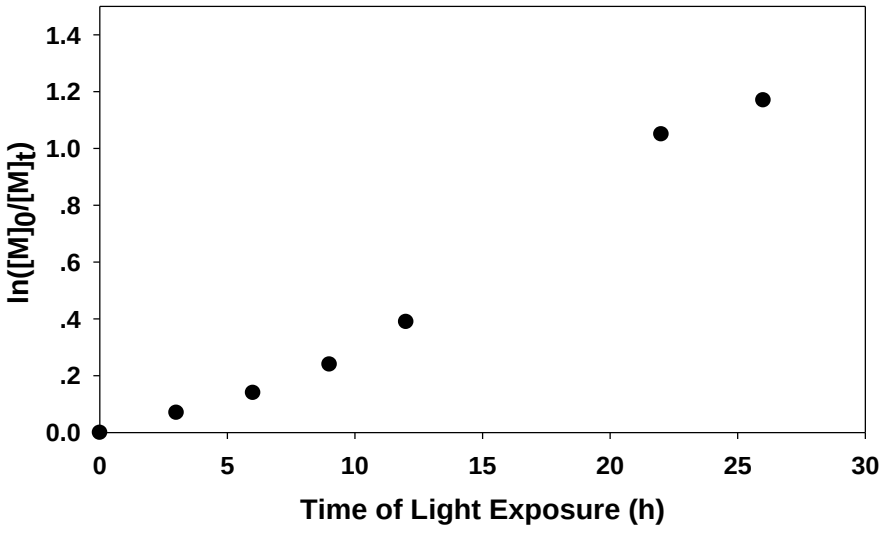


Figure 24. Plot of $\ln([M_n]/[M_t])$ versus time of radical polymerization using PIB-bound PTH **87** as a catalyst.

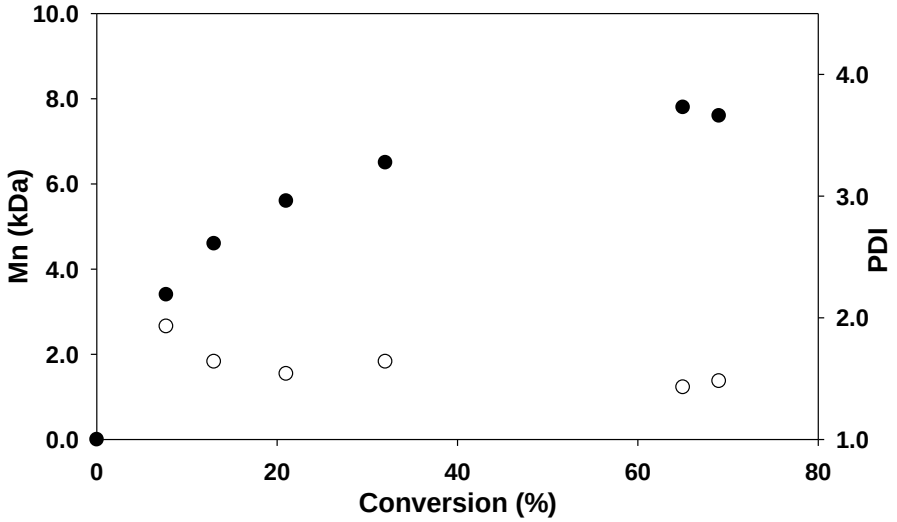


Figure 25. Plots of M_n (●) and PDI of **95** (○) versus conversion of **94** of radical polymerization using PIB-bound PTH **87** as a catalyst.

Finally, we analyzed the product polymers for catalyst contamination using ^{1}H NMR spectroscopy. To look for catalyst contamination in the poly(methyl methacrylate) or poly(2-ethoxyethyl methacrylate), we first looked at the aromatic region of the products' ^{1}H NMR spectra since the signals for the aromatic protons of **87** do not have any potential overlap with product polymer protons for polymers **90** and **92**. No contamination of **87** was detectable (^{1}H NMR spectra of the aromatic regions are shown in Figure 26 and 27). However, this analysis is somewhat insensitive since the *N*-phenylthiazine group in **87** is only ca. 20% of the mass of **87**. Moreover, the expected contamination level is low relative to the proton signals for PMMA or PEEMA, and the protons in question appear at multiplets. Fortunately, we were able to carry out a more sensitive ^{1}H NMR analysis for the presence of **87** in PMMA and PEEMA because the

signal for the protons of the 34 methyl groups in **87** that occurs at 1.14 δ does not overlap the methyl signals of PMMA or the methyl signals of PEEMA in the 0.5–2 δ region of the ^{1}H NMR spectrum.[131,132] A very small signal at ca. 1.14 δ was assumed to be due to **87** (cf. ^{1}H NMR spectra of the 0.5–2 δ regions in Figure 28-30). Integrating this signal versus the methyl protons of PMMA **90** at 0.86 and 1.03 δ, versus the methyl signals of PEEMA **92** at 0.92, 1.07, and 1.22 δ, or versus the methyl signals of PBnMA **95** at 0.75 and 0.94 δ showed that the wt% contamination of **87** in PMMA, PEEMA, and PBnMA was ca. 0.17 wt%, 0.45 wt% and 0.11 wt%, respectively. We also examined the products by GPC and did not see a peak for **87** in the GPC of any of the polymer products **90**, **92**, or **95**. However, we believe this GPC analysis is less sensitive than the ^{1}H NMR analysis.

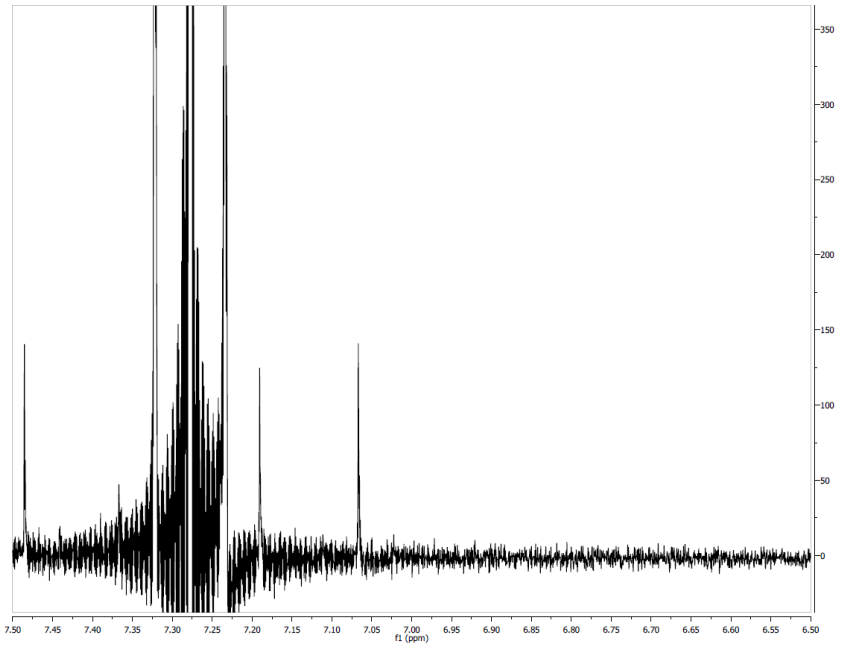


Figure 26. ^{1}H NMR spectrum of PMMA from 6.5 ppm to 7.5 ppm.

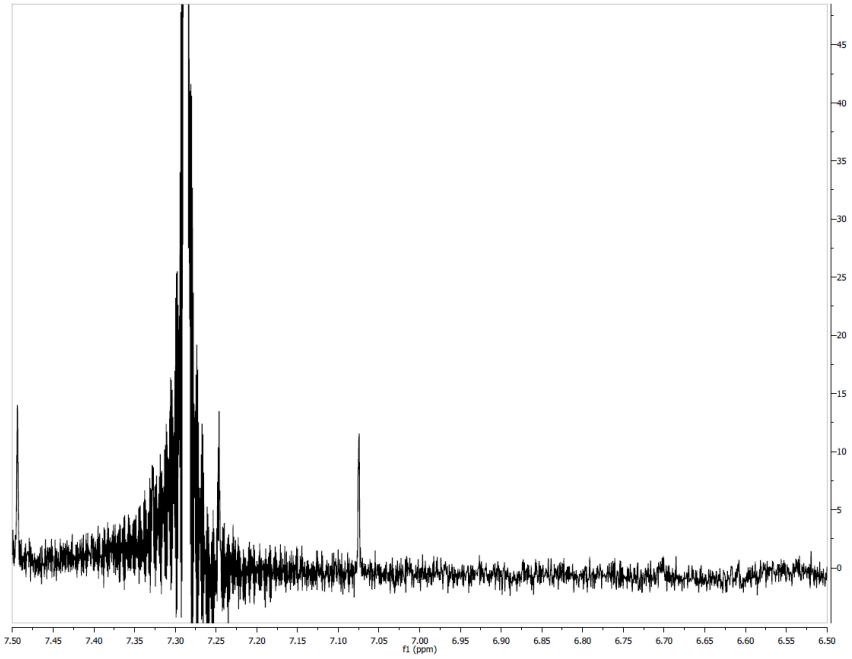


Figure 27. ^{1}H NMR spectrum of PEEMA from 6.5 ppm to 7.5 ppm.

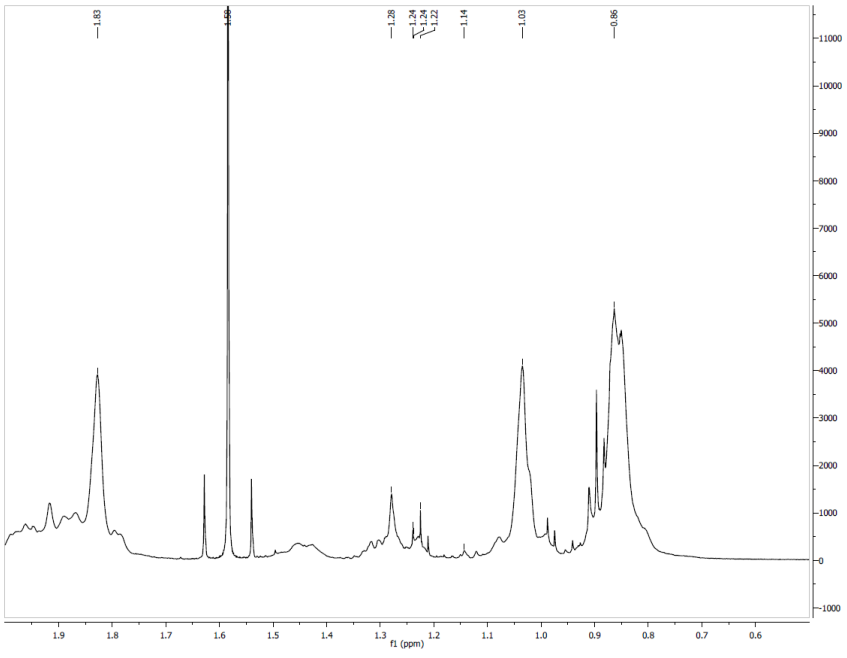


Figure 28. ^{1}H NMR spectrum of PMMA from 2.0 ppm to 0.5 ppm.

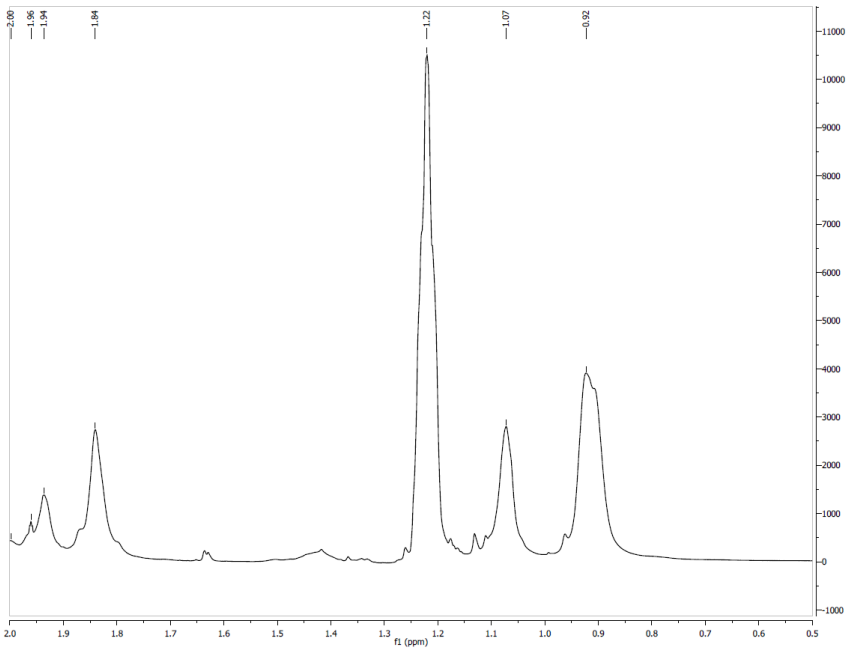


Figure 29. ^{1}H NMR spectrum of PEEMA from 2.0 ppm to 0.5 ppm.

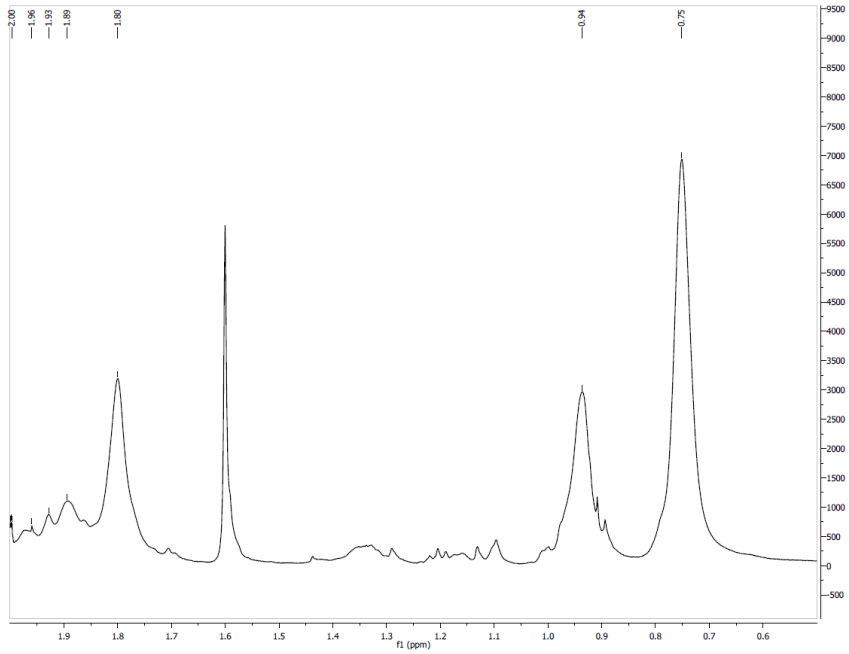


Figure 30. ^{1}H NMR spectrum of PBnMA from 2.0 ppm to 0.5 ppm.

Conclusions

In conclusion, a recyclable PIB-bound 10-phenylphenothiazine (PIB-PTH) polymerization catalyst can be readily prepared. This PIB-supported organo photoredox catalyst can be employed as a recyclable photoredox catalyst to carry out visible light-mediated radical polymerizations of a variety of acrylate monomers. Polymerizations can be effected in THF or a heptane/DMA solvent mixture and the catalyst can be recycled. As is true for a similar low molecular weight PTH catalyst, the polymerization reaction turns on with light irradiation and turns off in the dark. Kinetic studies of this PIB-bound PTH catalyzed photopolymerization showed that this PIB-bound organocatalyst could effect modest amount of control over the molecular weight and the molecular weight distribution of a polyacrylate product. This work shows that the strategy of a using soluble polymer support to recycle organic photoredox polymerization catalysts can supplement other work with PIB-supported transition-metal catalysts, providing a way to separate and recycle organo photocatalysts in polymer synthesis. These results also provide a synthetic route to PIB-bound organo photoredox catalysts that may be useful in other photoredox chemistry.

CHAPTER V

USING PHASE-SELECTIVELY SOLUBLE POLYISOBUTYLENE (PIB)-BOUND CATALYSTS TO FACILITATE HOMOGENEOUS CATALYSIS UNDER CONTINUOUS-FLOW SYSTEM

Introduction

In the past decades, the development of novel continuous-flow techniques for synthesis that are considered as environmentally benign synthetic pathways has become increasingly important and received heightened attention by synthetic chemists.[133-135] The applications of flow chemistry have been widely applied in the preparation of a wide variety of compounds,[136-139] such as fine chemicals, pharmaceutical ingredients, electronic materials. In traditional multi-step synthesis, reactions are commonly carried out in batch reactors with reagents added before the reaction, and the intermediates are isolated, and tedious work-up procedures are required in order to purify the products after each step. In contrast, reactions can be performed in a single stream in the continuous-flow process, and reagents are continuously introduced to the flow reactor, and the intermediates are directly transferred to the next reactor without isolation and are used in the subsequent reactions (Figure 31). Compared to the batch-wise synthesis, conducting chemical transformations in flow reactors has many advantages[140-143] including enhanced heat and mass transfer, optimized reaction conditions, simpler scale-up processes for a process, better reaction control, improved safety when handling hazardous intermediates, and simplified reaction and purification processes for multi-

step synthesis. Recent studies from a number of groups have demonstrated the advantages of applying continuous-flow techniques as useful tools in organic synthesis.

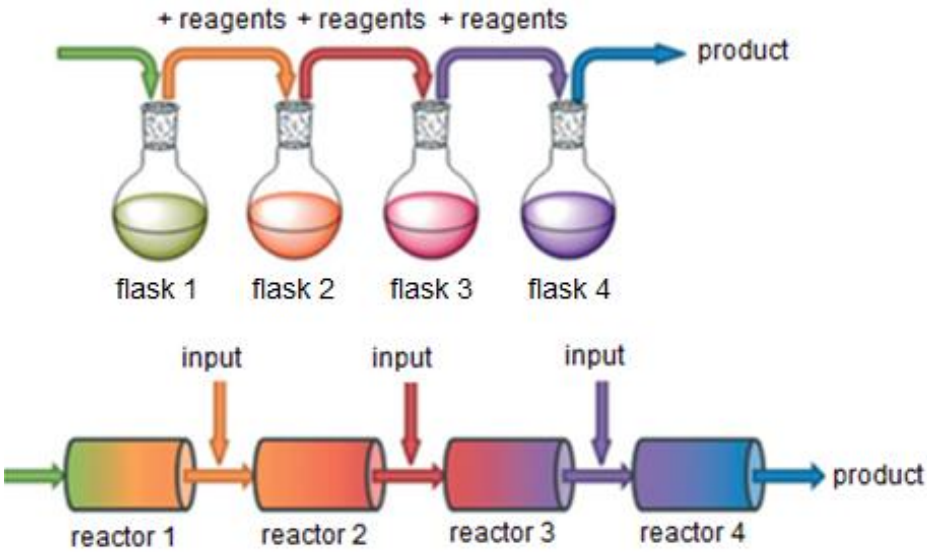
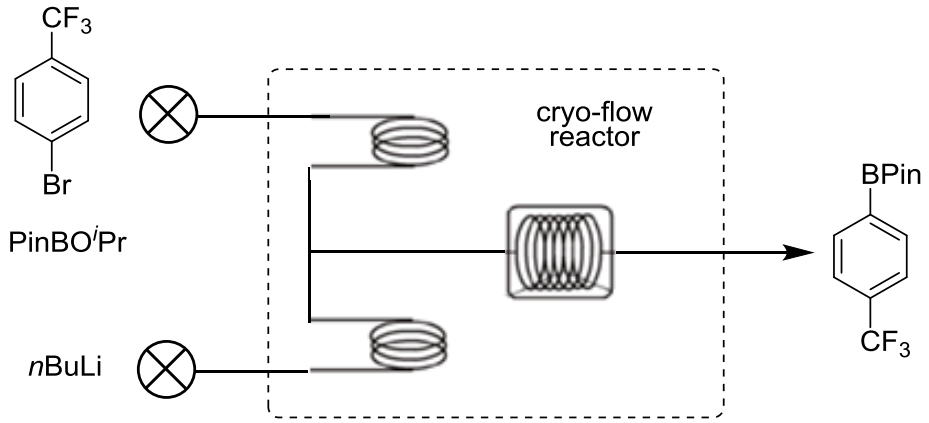


Figure 31. Batch-wise synthesis versus continuous-flow synthesis.

Ley's groups described a strategy for conducting reactions at low temperature in a flow reactor, which improved the reaction control during the process.[144] In that work, a cryogenic flow reactor was developed. This reaction allowed Ley's group to maintain the necessary low temperature for a long period of time without the use of external cryogenic sources. The utility of this cryogenic flow reactor was explored in the continuous synthesis of boronic acids and esters via lithium halogen exchange reactions at low temperature (Scheme 46). During the reaction, a solution of the aryl halide and boron substrates and a solution of *n*-BuLi were pumped into the reactor. In the initial experiment, the result showed that the process could only be carried out for 45 min. At

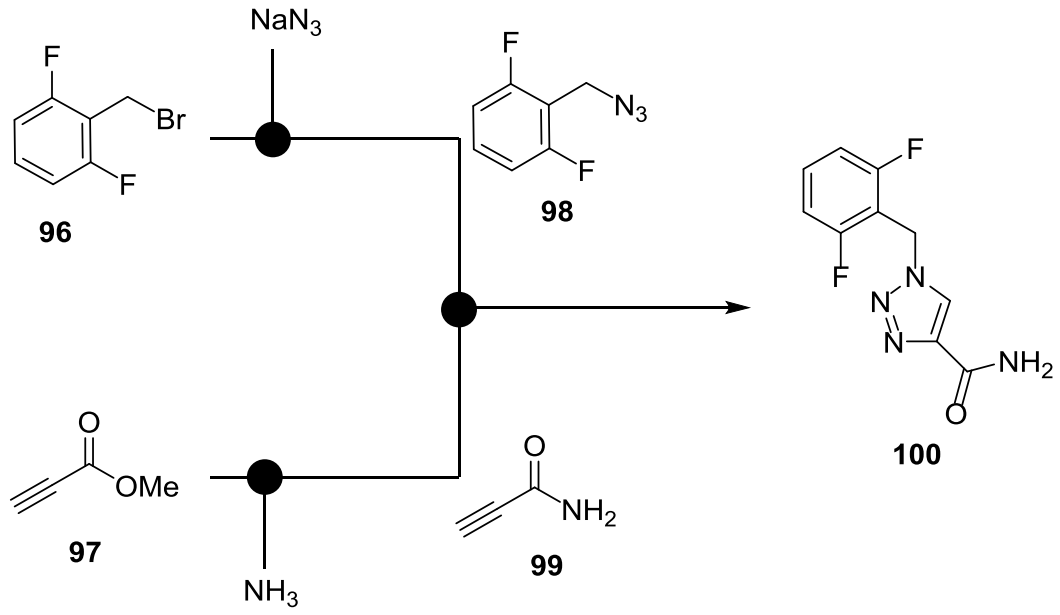
that point the reactor coil was blocked by a slurry of boronate complex. In order to solve this problem, a strategy to use *n*-BuLi directly from the reagent bottle through the piston pump heads was designed. Under this condition, the reaction could be performed at -60 °*C* for 5 h. After the reaction, the reaction mixture was collected and was treated with acid to afford the desired product in excellent yield and high purity without the necessity of a column purification.



Scheme 46. Flow synthesis of boronic esters using the cryogenic flow reactor.

In another example, Jamison and coworkers reported the use of continuous-flow synthesis of rufinamide.[145] Conventional methods for preparing such compounds often involve handling and isolation of toxic and explosive organoazide intermediates, a safety concern that limits the applications of this chemistry in industrial synthesis. In this case, the use of flow techniques enhanced the operation safety without accumulation and isolation of the azide intermediate. As shown in Scheme 47, the flow process started from the synthesis of 2,6-difluorobenzylazide **98** that was achieved via substitution of

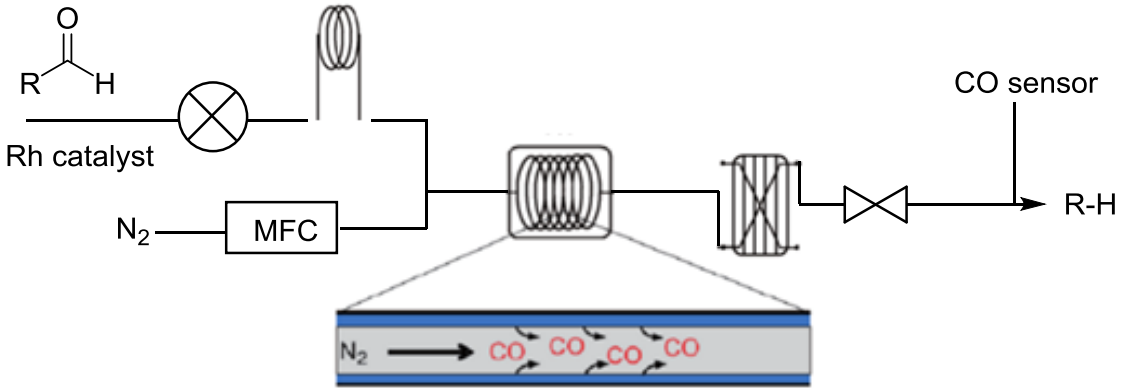
2,6-difluorobenzylbromide **96** with sodium azide at room temperature. Meanwhile, the propiolamide **99** was prepared from methyl propiolate **97** with high conversion. In this flow process, the unstable propiolamide was prepared in situ and was used immediately in the subsequent step under flow conditions. This avoids side reactions of this intermediate. Then the copper-tubing catalyzed [3 + 2] cycloaddition of intermediates **98** and **99** produced rufinamide **100** in 92% overall yield with an average residence time of 11 min.



Scheme 47. Continuous-flow synthesis of rufinamide.

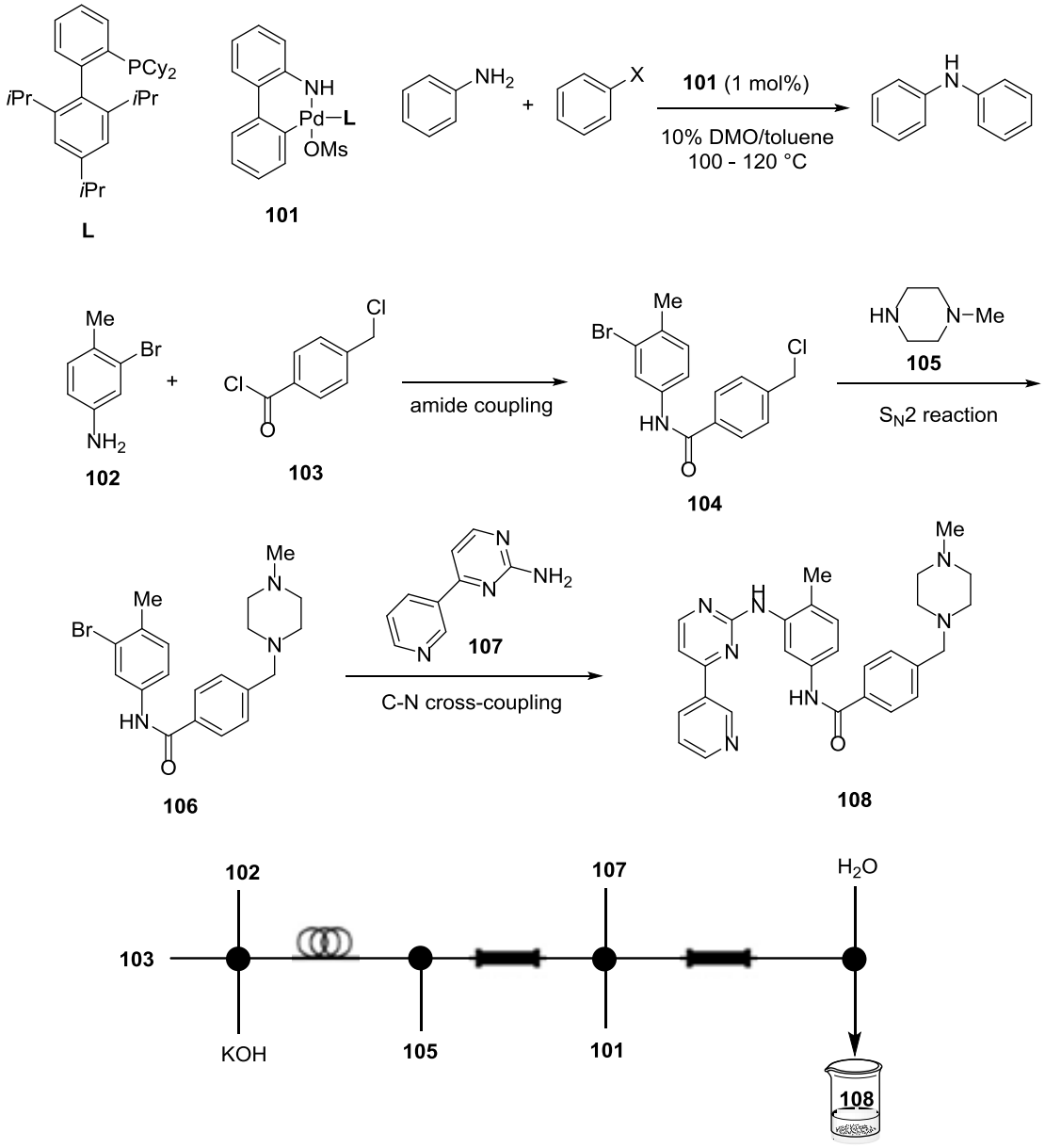
Kappe and coworkers developed a continuous-flow process for Rh-catalyzed decarbonylation of aldehydes,[146] which allows the reaction to be performed efficiently. In traditional batch synthesis, harsh reaction conditions and long reaction times often

lead to low product yields and make the scale-up of the reaction problematic. In this flow process, the reaction was performed with the aldehyde, $Rh(OAc)_2$, and the ligand, 1,3-bis(diphenylphosphino)propane (dppp) in toluene at 200 °*C* in a stainless-steel reactor with a flow rate of 0.3 mL/min (Scheme 48). During the reaction, the CO that is generated was removed from the reaction mixture by a stream of N_2 gas flow. This prevents catalyst poisoning and helps drive the equilibrium to the product using Le Châtelier's principle. A variety of aldehydes were investigated using this method, and the results showed that the desired decarbonylation products were obtained in excellent yields.



Scheme 48. Continuous-flow decarbonylation of aldehydes.

Buchwald and coworkers also demonstrated that flow chemistry is also feasible in C-N cross-coupling reactions.[147] In this work, they carried out a cross-coupling reaction using Brett-Phos precatalyst **101** and *N*,*N*-dimethyloctanamide (DMO) as a

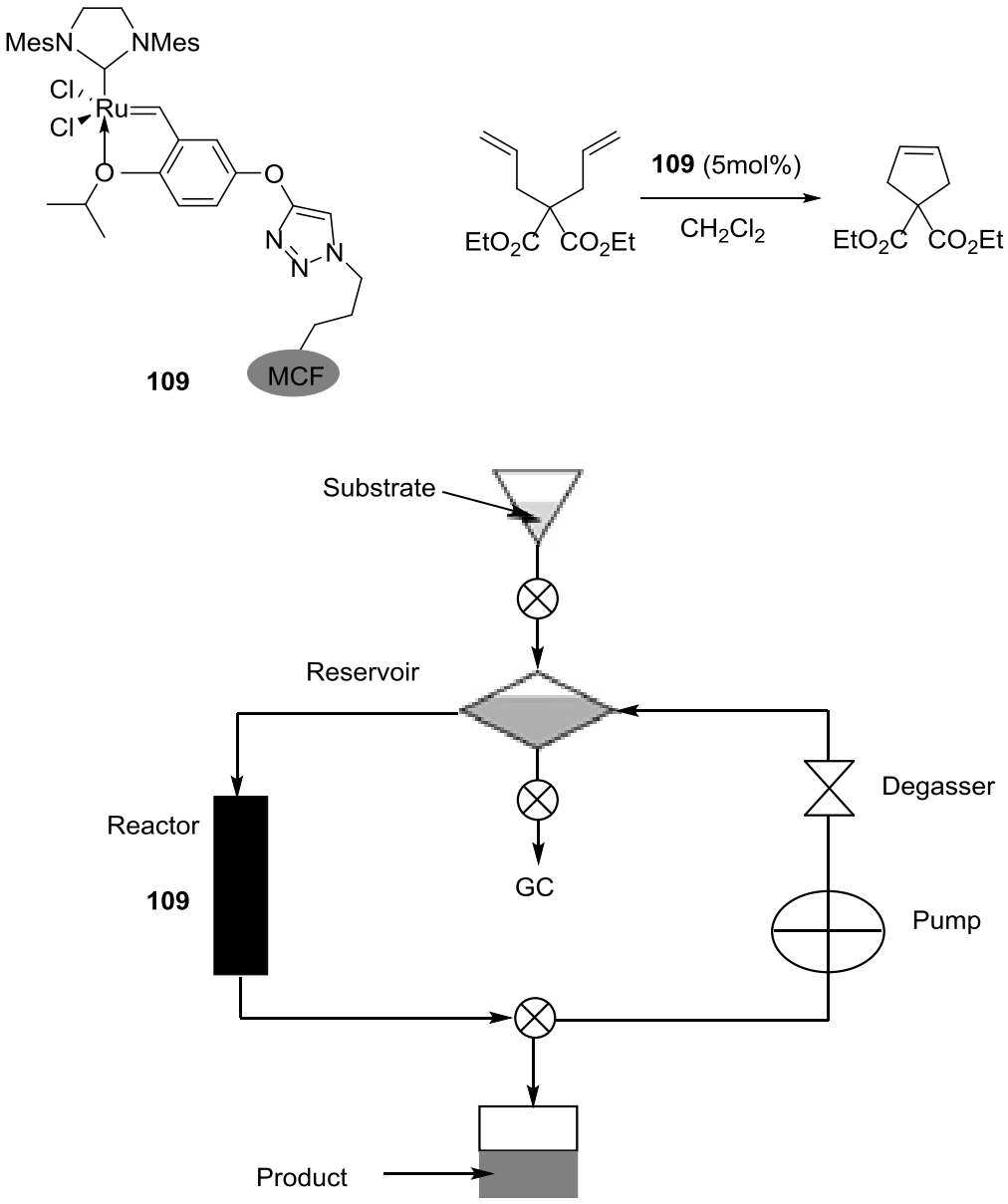


Scheme 49. Flow synthesis of biarylamines via C-N cross-coupling reactions and the three-step flow synthesis of imatinib.

cosolvent in a stainless steel packed-bed reactor (Scheme 49). Under these conditions, a series of aryl halides and aryl triflates were coupled with amine substrates producing the

corresponding products in excellent yields. In a traditional batch reaction, the triflation of phenol is usually conducted by slow addition of triflic anhydride to a solution of the phenol at low temperature. Flow chemistry allows this reaction to be efficiently carried out at ambient temperature. This flow strategy was further illustrated using a three-step synthesis of the cancer drug imatinib as an example. The synthesis began with the coupling of 3-bromo-4-methylaniline **102** with 4-chloro-methylbenzoyl chloride **103** to afford the amide **104**, followed with the nucleophilic substitution reaction with 1-methylpiperazine **105**. The last step in this synthesis was the C-N cross-coupling of **106** with 2-aminopyrimidine **107**. During the flow process, the reaction mixture from the previous reactor was transferred to the next reactor used directly without purification. The total residence time of the three-step synthesis was less than 35 min, and the imatinib **108** was isolated in 56% yield.

Immobilized catalysts have also been used in continuous-flow synthesis.[148,149] Lim *et al.* reported using a supported Ru catalyst to carry out a ring closing metathesis (RCM) reaction in a flow system (Scheme 50).[150] In this case, a recyclable silica-immobilized Hoveyda-Grubbs catalyst **109** was prepared through click chemistry. The catalyst was first examined in RCM of dienes in the batch reactor and showed good activity and recyclability. Then the chemistry was investigated in a continuous-flow process. In this flow process, the solution of diene substrate was introduced to the flow reactor that contained the catalyst **109**. The result showed that the conversion decreased

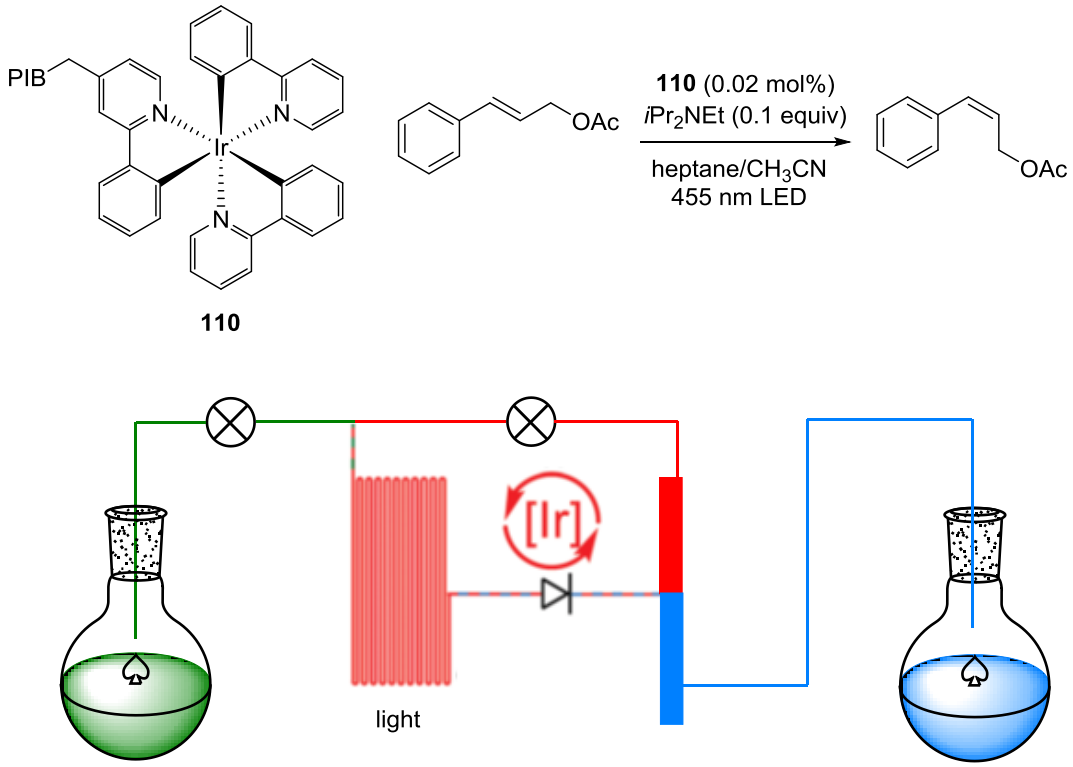


Scheme 50. Continuous-flow RCM using silica-supported Grubbs catalyst.

during the process because the in situ generated ethylene deactivated the catalyst. To address this problem, a circulating flow system was developed, in which the reaction mixture was circulated in the system, and the ethylene was removed from the reactor by

degasser that minimized the catalyst deactivation. The results showed that over 95% of the diene was converted to the product with a turnover frequency of 1.5 min^{-1} that was 5 times higher than a batch reaction. In addition, the ICP-MS analysis indicated that the Ru leaching was 4.3% for a turnover number (TON) of 100.

In 2016, Reiser and coworkers reported an example of using a soluble polymer-supported Ir(III) photoredox catalyst in a flow system.[151] In their work, the catalyst was continuously recycled so as to reduce the amount of iridium catalyst that was needed as compared to the batch process. A PIB-bound iridium complex $Ir(ppy)_2$(PIB-ppy) **110** was prepared and showed excellent catalytic activity. Photocatalyzed *E/Z* isomerization of alkene was then carried out in a continuously-flow system using this polymer-supported catalyst (Scheme 51). In this process, a heptane-saturated acetonitrile solution of reagents and a heptane solution of **110** were pumped into a transparent reactor. Upon heating, the biphasic solvent mixture became a homogeneous solution that was irradiated with light. After the reaction was completed, the reaction mixture was transferred to a phase separation unit where the two phases separated, and the catalyst-containing heptane phase was reused, while the product-containing acetonitrile was isolated. The results showed high conversion of the *E*-alkene. Iridium leaching was shown to be 2.6% of the charged catalyst at the beginning of the reaction and decreased to below 0.1% during reaction based on ICP-OES analysis. The reaction was also examined under the biphasic condition at ambient temperature at a slower flow rate, and the results indicated that there was no significant change of the activity.



Scheme 51. Visible light-mediated *E/Z* isomerization using PIB-bound iridium complex in a continuous-flow process.

A general thrust of research in the Bergbreiter's group is the development of green synthetic strategies, especially the recovery and reuse of homogeneous catalysts. Extensive studies have shown that the systems can be devised where a catalytic reaction can be carried out under homogeneous condition by taking the advantages of soluble polymer-supported catalysts. This process can be carried out in mixed solvents and the catalyst can be separated from the product and recovered from a biphasic solvent mixture after the reaction.[10,24] However, all of these studies previously have been conducted under batch conditions. Therefore, developing a strategy to use these soluble

polymer-supported catalysts in catalytic reactions under flow conditions that enable the catalyst recycling without manual separation gained our interest. In this chapter, we explore the potential for the use of these recyclable catalysts in a continuous-flow process, in which the catalyst can be separated and reused constantly. The results described below showed that the phase-selectively soluble polymer support can facilitate the catalyst/product separation in the flow system, which simplified the processes for recycling and reuse of the catalyst. The PIB-bound transition-metal catalysts that were examined in cylopropanation and RCM reactions showed modest catalytic activity and recyclability.

Results and Discussion

In order to investigate catalytic reactions in flow with soluble polymer-supported catalysts, we first designed a continuous-flow reaction system (Figure 32). In this system, the substrates and the PIB-supported catalyst were pumped into the Teflon tubes and combined together at a T-shape connector where the reaction started. The reaction mixture flowed in the tube and was transferred to a separatory funnel that contains a polar solvent like acetonitrile. In the funnel, the product was extracted into the bottom polar acetonitrile phase, and the top catalyst-containing heptane phase was pumped back to the system for the next reaction run. At the end of the process, the product-containing acetonitrile phase was collected and concentrated under reduced pressure to afford the crude product. The pure product could be isolated by further purification if required.

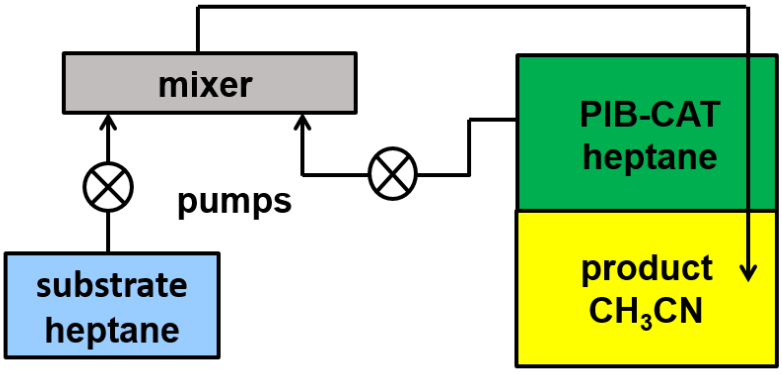
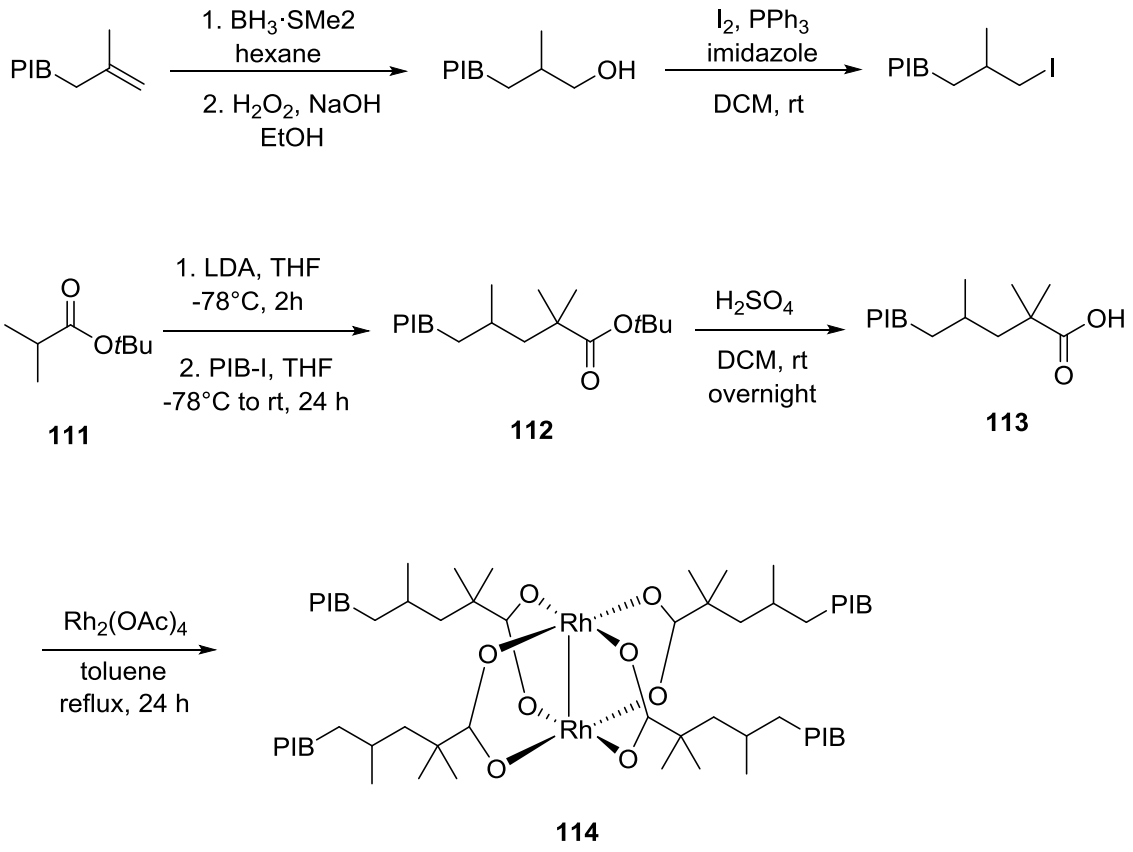


Figure 32. General scheme of the continuous-flow reaction system.

Having this flow reaction system, we first explored its utility in Rh-catalyzed cyclopropanation chemistry we had previously studied in a batch reactor. This chemistry used a heptane-soluble PIB-bound Rh(II) carboxylate complex **114** that was prepared as shown in Scheme 52. In this case, we developed a more straightforward synthetic pathway for the preparation of PIB-bound carboxylic acid than was previously reported.[152] Using the ester enolate chemistry shown in Scheme 52, a carboxylic acid terminated PIB ligand was synthesized with no presence of other functional groups. The synthesis started with the vinyl terminated PIB (M_n = 2300 Da), and the PIB-bound iodide was prepared following our previously described procedures.[153] Then *tert*-butyl isobutyrate **111** was deprotonated using LDA in THF at -78 °C, and the generated anion was then allowed to react with PIB-bound iodide to afford the PIB-bound *tert*-butyl ester **112**. The ester **112** cleavage was carried out in the presence of H_2SO_4 in dichloromethane at room temperature to produce the PIB-bound carboxylic acid ligand **113**. Finally, the PIB-bound Rh(II) carboxylate complex **114** was prepared by ligand

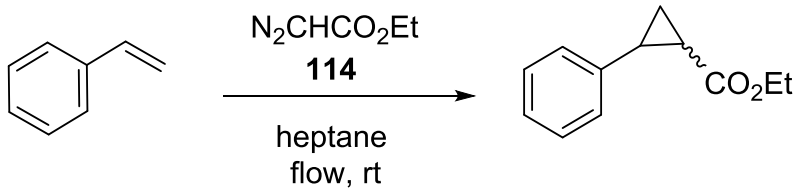
exchange reaction of PIB-bound carboxylic acid ligand **113** with $Rh_2(OAc)_4$ in refluxing toluene to afford the product as a dark green viscous oil with a Rh loading of 0.098 mmol/g that was determined based on ICP-MS analysis.



Scheme 52. Synthesis of the PIB-bound Rh(II) carboxylate complex **114**.

Having the PIB-bound Rh(II) complex in hand, we used it as a recyclable catalyst for cyclopropanation of styrene under continuous-flow condition (Scheme 53). As shown in Figure 33, the flow reaction was carried out with a heptane solution of catalyst **114** that was pumped into the system using an HPLC pump at a flow rate of 0.05

mL/min, while the mixture of ethyl diazoacetate and styrene was introduced into the system using a syringe pump at a flow rate of 0.4 mL/h. During the reaction, an efficient separation of the catalyst-containing heptane phase from the product-containing acetonitrile phase was observed (Figure 34). The catalyst-containing heptane phase was pumped back to the system and kept catalyzing the reaction. The continuous reaction was run at ambient temperature for 31 h. The results showed that the reaction was successfully carried out under this condition and that the starting material was converted to the product. After the reaction was completed, the crude product was purified by column chromatography to afford the desired cyclopropanation product in 68% isolated yield. The formation of the dimeric by-products occurred to the extent of 9% based on ^{1}H NMR spectroscopy analysis.



Scheme 53. PIB-bound Rh(II) complex catalyzed cyclopropanation of styrene in flow.

As shown in Table 6, these results are comparable to the previous results of batch reactions using the PIB-bound Rh(II) catalyst in a heptane/acetonitrile biphasic solvent mixture.[152] In addition, the rhodium leaching level was determined by ICP-MS analysis of the crude product and showed 1.8% of the charged catalyst leached into the product phase during the flow process. This experiment indicated that the phase-selectively

soluble PIB-bound Rh(II) complex could catalyze the cyclopropanation reaction in a continuous-flow system with increased reaction scale and gave the product in satisfactory yield with modest dimers formation of the diazo substrate.

Table 6. Results of the styrene cyclopropanation reaction catalyzed by the PIB-bound Rh(II) complex **114**.

Entry	EDA (mmol)	Yield [%][c]	TOF (h^{-1})	Dimer Yield [%][d]
Flow[a]	5.25	68	5.5	9
batch[b]	2	65[e]	6.5	7

[a]The reaction was carried out using 5.25 mmol of EDA and 19 equiv of styrene with a 15 mL heptane solution containing 0.4 mol% of **114** at RT in the flow system. [b]The reactions were carried out using 2 mmol EDA with 0.5 mol% of **42** and 10 equiv of styrene using a 5 mL/15 mL mixture of heptane/CH_3CN at RT for 20 h. [c]Yields of the isolated cyclopropanation product. [d]Yields of maleate/fumarate by-products were determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [e]Average isolated yields of 3 cycles.

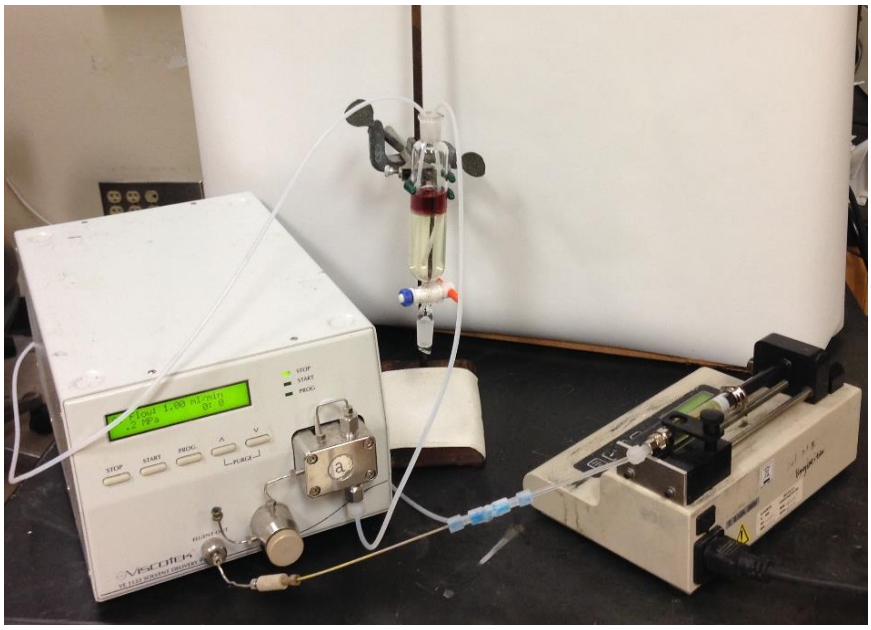
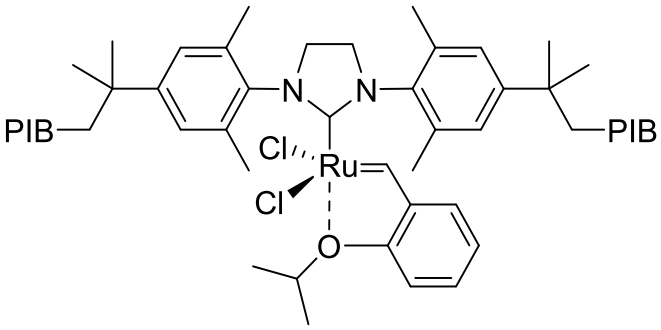


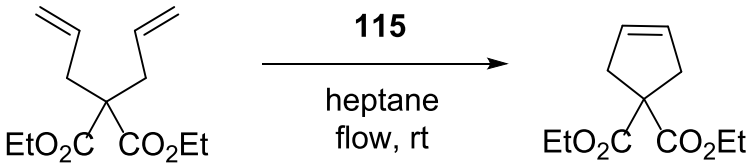
Figure 33. Continuous-flow reaction and separation system set up.

Figure 34. Catalyst-containing phase (top) and product-containing phase (bottom) separation in the continuous-flow cyclopropanation reaction using PIB-bound Rh(II) complex.

With the success of conducting the styrene cyclopropanation reaction under flow conditions, we aimed to apply this continuous-flow system in other PIB-supported transition-metal catalyst mediated reactions in order to explore the generality of this strategy. To do this, we prepared a PIB-bound Hoveyda-Grubbs second generation catalyst that we had successfully demonstrated to be a recyclable catalyst in batch RCM reactions and examined its use under flow conditions. The necessary PIB-bound Hoveyda-Grubbs second generation catalyst **115** was prepared following a literature procedure.[154] An ICP-MS analysis showed a Ru loading of 0.19 mmol/g for catalyst **115**.



115



Scheme 54. PIB-bound Hoveyda-Grubbs second generation catalyst catalyzed RCM of diethyl diallylmalonate in flow.

With the catalyst in hand, we then used **115** to carry out RCM of diene in our continuous-flow reactor. The reaction was performed similarly as the previously described cyclopropanation chemistry. The heptane solution of catalyst **115** was pumped into the system using an HPLC pump at a flow rate of 0.05 mL/min, and the heptane solution of diethyl diallylmalonate was introduced into the system using a syringe pump at a flow rate of 0.3 mL/h. This reaction was run at ambient temperature for 18.3 h. Under this condition, the results showed that 77% of starting diene substrate was converted to the corresponding product, diethyl 3-cyclopentene-1,1-dicarboxylate. As can be seen in Table 7, these results are less comparable to our previously reported results using catalyst **115** in heptane under batch condition. The possible reason for the lower conversion observed could be due to the less efficient removing of the in situ generated ethylene during the reaction that effected the active ruthenium catalyst.[149,155]

In addition, the Ru leaching was determined by ICP-MS analysis of the crude product and showed that 6.1% of the charged catalyst leached into the product phase. The relatively high leaching level indicated that some of the catalyst could be decomposing during this process. This may reflect the instability of the methylidene intermediate. Nonetheless, this experiment showed that the phase-selectively soluble PIB-bound Hoveyda-Grubbs second generation catalyst could effect the RCM reaction in a continuous-flow system. To further improve the catalytic performance of this chemistry, the use of a degasser could be introduced so that the ethylene can be removed from the flow system. It may also be necessary to carry out the chemistry under more rigorous oxygen-free conditions.

Table 7. Results of the RCM reaction catalyzed by the PIB-bound Hoveyda-Grubbs second generation catalyst 115.

Entry	Diene (mmol)	TOF (h^{-1})	Yield [%]
Flow[a]	5	3.3	73[c]
batch[b]	0.5	16.4	82[d]

[a]The reaction was carried out using a solution of 5 mmol of diethyl diallylmalonate in 4 mL of heptane with a 15 mL heptane solution containing 1.2 mol% of **115** at RT in the flow system. [b]The reactions were carried out using 0.5 mmol of diethyl diallylmalonate with 5 mol% of **115** in 5 mL of heptane at RT for 1 h. [c]Yield was determined based on conversion. [d]Average isolated yields of 5 cycles.

Conclusions

In conclusion, a new synthetic route for the preparation of PIB-bound carboxylic acid was described. Moreover, a continuous-flow reaction system has been developed, and its utility in homogeneous catalysis was explored using PIB-bound transition-metal catalysts. The PIB-bound Rh complex catalyzed styrene cyclopropanation reaction was carried out in this flow system. The results indicated that the desired products were obtained in satisfactory yield with a moderate level of the byproducts formation. PIB-bound Hoveyda-Grubbs catalyst catalyzed RCM reactions using the flow system was also examined. In these studies, constantly reuse of the catalysts was achieved by taking the advantage of PIB's excellent phase selective solubility. Application of this approach in other soluble polymer-supported organocatalysts catalyzed reactions is under investigation. The success in the use of soluble polymer-supported catalysts in flow chemistry provides an environmentally benign synthetic pathway.

CHAPTER VI

EXPERIMENTAL SECTION

Materials and Instrumentation

Vinyl terminated PIB (Glissopal) with a molecular weight of 1000 Da or 2300 Da was provided by BASF.[49] Styrene was passed through a plug of neutral alumina before use. Methyl methacrylate, 2-ethoxyethyl methacrylate, and benzyl methacrylate were passed through a plug of basic alumina before use. Other reagents and solvents were purchased from commercial suppliers and used without further purification unless otherwise stated. All glassware was oven-dried or flame-dried before use. Fittings and connectors for the construction of the flow reactor were purchased from IDEX Health & Science. Gastight syringes were purchased from Hamilton Company. A Viscotek VE1122 Solvent Delivery System was used to pump the catalyst in the continuous-flow system. ^{1}H NMR and ^{13}C NMR spectra were obtained on either an Inova 300 spectrometer operating at 299.91 MHz for proton and 75.41 MHz for carbon nuclei, or an Inova 500 spectrometer operating at 499.95 MHz for proton and 125.72 MHz for carbon nuclei at room temperature. Chemical shifts are reported in parts per million (ppm) (δ) relative to the residual proton resonances in $CDCl_3$, and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), m (multiplet), and bs (broad singlet). GPC data were collected using a Viscotek LT4000L mixed bed column in THF solvent. The Viscotek instrument was equipped with a VE 3210 UV-Vis detector, a 270 Viscometer and Light Scattering Dual detector,

and a VE 3580 RI detector. The molecular weights and PDI of the polymers were determined using the OmniSEC software (v. 4.7) based on polystyrene standards. Melting points were measured by Stanford Research Systems OptiMelt apparatus and uncorrected. IR spectra were obtained using a Shimadzu IRAffinity-1S FTIR spectrophotometer. UV-Vis spectra were obtained using a Shimadzu UV-2600 spectrometer. A PerkinElmer's NexION 350 ICP-MS spectrometer was used to determine metal loading in the catalyst and crude products.

Synthesis and Experimental Procedures

Synthesis of PIB-bound carboxylic acid (41). A 250-mL round-bottomed flask was equipped with a magnetic stir bar, and PIB-phenol (3.7 g, 1.52 mmol), ethyl 11-iodoundecanoate (1.4 g, 4.4 mmol), potassium *tert*-butoxide (0.9 g, 8 mmol), and THF (100 mL) were added to the flask. Then the reaction mixture was allowed to reflux under nitrogen for 36 h. The reaction mixture was cooled to room temperature, hexane (100 mL) and water (25 mL) were added to reaction mixture. The hexane phase was separated and washed with acetonitrile (25 mL) for 3 times. The hexane layer was dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to obtain crude PIB-bound ester **40** as a viscous oil. At this point, the PIB-bound ester **40** (2.6 g, 0.97 mmol), sodium hydroxide (0.9 g, 23 mmol), THF (50 mL) and water (15 mL) were added to a 100-mL round-bottomed flask equipped with a magnetic stir bar. Then the reaction mixture was allowed to reflux under nitrogen for 24 h. The reaction mixture was cooled to room temperature, and HCl solution was added to reaction mixture. Then the

reaction mixture was extracted with hexane (50 mL) for 3 times. The hexane layers were combined and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to obtain crude PIB-bound carboxylic acid **41** as a viscous oil. This crude product was purified by silica gel column chromatography using hexane/ethyl acetate (10:1, v/v) as the eluent to obtain the final product (2.2 g, 56% yield). ^{1}H NMR (300 MHz, CDCl3) δ: 7.27 (d, 2 H), 6.84 (d, 2 H), 3.95 (t, 2 H), 2.38 (t, 2H), 1.75-0.65 (m); ^{13}C NMR (125 MHz, CDCl3) δ: 177.5, 156.7, 142.3, 127.0, 113.6, 67.9, 59.5-58.0 (multiple peaks), 38.0-11.5 (multiple peaks).

Synthesis of PIB-bound Rh complex (42). A 100-mL round-bottomed flask equipped with a stir bar was charged with PIB-bound carboxylic acid **41** (1.8 g, 0.69 mmol) and rhodium acetate (65 mg, 0.15 mmol) dissolved in toluene (50 mL). This solution was stirred at 80 °C under nitrogen for 24 h. Then the reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The viscous oil obtained was dissolved in hexane (50 mL) and washed with 90% ethanol/water (20 mL) for three times. The hexane layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to obtain PIB-bound Rh complex **42** as dark green viscous oil in 91% yield. Complex **42** was characterized by UV-vis (EtOH/toluene) λ_{max} = 588 nm. The ε value for **42** was based on a comparison to the absorbance of $Rh_2(OAc)_4$ (λ_{max} = 587 nm, ε = 260 M-1cm-1) in the same 50/50 (vol/vol) mixture of ethanol and toluene. The extinction coefficient of $Rh_2(OAc)_4$ was used to calculate a loading of 0.167 mmol of Rh/g for **42** (M_n = 1.2 × 10^4 g/mol) based on the

absorbance of a solution of 11.2 mg of **42** in 5 mL of this EtOH/toluene solution. This M_n is consistent with **42** containing 4 PIB_{2300} groups.

General procedure for cyclopropanation of styrene. A 50-mL round-bottomed flask equipped with a stir bar was charged with styrene (2.1 g, 20 mmol), and ethyl diazoacetate (0.23 g, 2 mmol) in acetonitrile (15 mL). PIB-bound Rh complex **42** (120 mg, 10 μmol) was dissolved in heptane (5 mL), and this heptane solution was added to the flask. The reaction mixture was allowed to stir at ambient temperature for 20 h. To the extent possible, reactions from run to run were stirred at similar rates using a magnetic stirrer. Then the biphasic mixture was transferred to a separatory funnel, the bottom acetonitrile phase was separated, and the heptane layer was washed with acetonitrile (5 mL) for two times. The heptane phase was recovered and reused for the following cycle, and the acetonitrile phases were combined and removed under reduced pressure. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate (10:1, v/v) as the eluent to obtain the final product as a mixture of diastereomers. Both are known compounds and the NMR data obtained agreed with the spectral data in the literature.[156]

***cis*-2-Phenylcyclopropane-1-carboxylic acid ethyl ester**: ^{1}H NMR (300 MHz, CDCl3) δ : 7.26 (m, 5H), 3.90 (q, 2H), 2.61 (q, 1H), 2.11 (m, 1 H), 1.74 (m, 1H), 1.36 (m, 1H), 1.00 (t, 3H); ^{13}C NMR (125 MHz, CDCl3) δ (ppm): 171.0, 136.5, 129.3, 127.9, 126.7, 60.3, 25.5, 21.9, 14.1, 11.2.

***trans*-2-Phenylcyclopropane-1-carboxylic acid ethyl ester**: ^{1}H NMR (300 MHz, CDCl3) δ: 7.30 (m, 3H), 7.14 (dd, 2H), 4.21 (q, 2H), 2.56 (m, 1 H), 1.94 (m, 1H), 1.64 (m, 1H), 1.32 (t, 4H); ^{13}C NMR (125 MHz, CDCl3) δ: 173.5, 140.1, 128.5, 126.5, 126.2, 60.8, 26.4, 24.2, 17.0, 14.1.

General procedure for O-H insertion of isopropanol. A 50-mL round-bottomed flask equipped with a stir bar was charged with isopropanol (1.2 g, 20 mmol), and ethyl diazoacetate (0.23, 2 mmol) in acetonitrile (15 mL). PIB-bound Rh complex **42** (120 mg, 10 μmol) was dissolved in heptane (5 mL), and this heptane solution was added to the flask. The reaction mixture was allowed to stir at ambient temperature for 20 h. Then the biphasic mixture was transferred to a separatory funnel, the bottom acetonitrile phase was separated, and the heptane layer was washed with acetonitrile (5 mL) for two times. The heptane phase was recovered and reused for the following cycle, and the acetonitrile phases were combined and removed under reduced pressure. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate (15:1, v/v) as the eluent to obtain 0.45 g of the final product whose NMR spectral agreed with the spectral data in the literature.[157]

Ethyl 2-isopropoxyacetate: ^{1}H NMR (300 MHz, CDCl3) δ (ppm): 4.21 (q, 2H), 4.06 (s, 2H), 3.68 (m, 1H), 1.28 (t, 4 H), 1.21 (d, 6H); ^{13}C NMR (125 MHz, CDCl3) δ (ppm): 170.8, 72.5, 65.7, 60.7, 21.6, 14.1.

Kinetic study of EDA dimerization in dichloromethane. A 20-mL vial was equipped with a magnetic stir bar, and ethyl diazoacetate (89 mg, 0.08 mmol), $Rh_2(OAc)_4$ (1.8 mg, 0.5 mol%) and dichloromethane (2 mL) were added to the vial. The reaction was stirred at ambient temperature, and aliquots of the reaction mixture were removed after 10 min and were analyzed by ^{1}H NMR spectroscopy using an internal standard to measure the amount of starting materials and products at various times.

Kinetic study of EDA dimerization in CH_2Cl_2/CH_3CN monophasic system. A 20-mL vial was equipped with a magnetic stir bar, ethyl diazoacetate (83 mg, 0.073 mmol), $Rh_2(OAc)_4$ (1.6 mg, 0.5 mol%), acetonitrile (1 mL) and dichloromethane (1 mL) were added to the vial. The reaction was stirred at ambient temperature, and aliquots of the reaction mixture were removed at different time points. A known amount of 1,1,2,2-tetrachloroethane was added as an internal standard, and all the samples were analyzed by ^{1}H NMR spectroscopy using an internal standard to measure the amount of starting materials and products at various times.

Kinetic study of EDA dimerization in CH_3CN monophasic system. A 20-mL vial was equipped with a magnetic stir bar, and ethyl diazoacetate (0.11 g, 0.096 mmol), $Rh_2(OAc)_4$ (2.3 mg, 0.5 mol%) and acetonitrile (2 mL) were added to the vial. The reaction was stirred at ambient temperature, and aliquots of the reaction mixture were removed at different time points. A known amount of 1,1,2,2-tetrachloroethane was added as an internal standard, and all the samples were analyzed by ^{1}H NMR

spectroscopy using an internal standard to measure the amount of starting materials and products at various times.

Kinetic study of EDA dimerization in heptane/CH_3CN biphasic system. A 20-mL vial was equipped with a magnetic stir bar, and ethyl diazoacetate (93 mg, 0.081 mmol), PIB-bound Rh catalyst **42** (47 mg, 0.5 mol%), heptane (1 mL) and acetonitrile (3 mL) were added to the vial. The reaction was stirred at ambient temperature, and aliquots of the reaction mixture were removed at different time points. A known amount of 1,1,2,2-tetrachloroethane was added as an internal standard, and all the samples were analyzed by ^{1}H NMR spectroscopy using an internal standard to measure the amount of starting materials and products at various times.

Phase selective solubility studies of EDA in heptane/CH_3CN. A 20-mL vial was equipped with a magnetic stir bar, and ethyl diazoacetate (0.175 g, 1.53 mmol), heptane/PIB (2 mL) and acetonitrile (6 mL) were added to the vial. The biphasic mixture was stirred at ambient temperature for 4.5 h, and aliquots of the reaction mixture were removed from both heptane and acetonitrile phases. A known amount of 1,1,2,2-tetrachloroethane was added as an internal standard, and all the samples were analyzed by ^{1}H NMR spectroscopy using an internal standard to measure the amount of ethyl diazoacetate in both phases.

Procedure for anti-leaching study of PIB-bound Ru Complex. A PIB-bound Ru complex (80 mg) was dissolved in 4 mL of heptane in a 20-mL vial at ambient temperature. Then, 2 mL of ethanol, and 3 mL of DMF were added, and the ternary solvent mixture was heated to 90 ˚C to form a homogeneous solution. After heating, the solution was cooled to room temperature and a biphasic system reformed. This biphasic mixture was composed of a dark red heptane-rich phase and a slightly reddish polar phase. Then this solvent mixture was reheated and 0.4 g of PIB_{2300} was added to the hot solution. Subsequent cooling to room temperature reformed a biphasic system whose polar phase was visually colorless showing that the leaching of the PIB-bound Ru complex **44** into the polar phase decreased.

Phase selective solubility studies of PIB_{2300} azo dye. A PIB-bound azo dye (0.03 g) prepared by following a reported procedure[80] was dissolved in 3.0 g of heptane, aPP, or a heptane-aPP solvent mixture (2:1 wt:wt). aPP is a relatively low molecular liquid polypropylene polymer obtained from Baker Hughes (M_n = 700 Da). After dissolution of the dye in the nonpolar solvent, 3.0 g of methanol was added, and the biphasic solvent system was heated to 90 ˚C in a sand bath with stirring to fully or partially (in the case of aPP) miscibilize the nonpolar solvent with methanol. After heating, the solution was cooled to room temperature and a biphasic system was reformed. The methanol layer was analyzed by UV-visible spectroscopy to determine leaching of the polymer azo dye **43**.

Procedure for NMR experiments used to determine leaching of PIB_{1000} into the polar phase of a cyclohexane/polar solvent mixture. 2 g of PIB_{1000} was dissolved in 5 g of cyclohexane and the resulting solution was added to 5 g of a polar solvent (methanol or DMF). The resulting biphasic mixture was stirred vigorously overnight at ambient temperature. Allowing the solution to stand produced a biphasic mixture. A sample of the polar solvent phase was then dissolved in $CDCl_3$. The ^1H NMR spectroscopic analysis was carried out on a 500 MHz spectrometer. In this analysis, the cyclohexane and the polar solvent peaks could be integrated and compared to peaks for polyisobutylene. The molarity of the polyisobutylene was determined by comparison with the integral values for the satellite peaks of cyclohexane and the polar solvent, taking into account the relative amounts of each present in the solution. Typically other minor solvent impurity peaks were present but did not compromise the ability of the significant peaks to be identified since in all cases at least one of the polyisobutylene peaks could be analyzed. Using either DMF or methanol as the polar solvent in a cyclohexane/polar solvent mixture, the molarity of PIB in the polar phase was determined to be 7×10^{-4} M (< 4 mg/5 mL).

Synthesis of PIB-bound bipyridine ligand (49). A 100-mL round-bottomed flask was equipped with a magnetic stir bar and sealed with a rubber septum. Then 10 mL of distilled anhydrous THF was transferred into the flask by forced siphon. The THF was cooled to -78 °C. Diisopropylamine (0.46 mL, 3.3 mmol) was added by syringe, followed by the addition of 2.5 mL of a 1.6 M solution of *n*-butyllithium in hexane (4

mmol). After stirring for 45 min, a solution of 4,4'-dimethyl-2,2'-bipyridine 48 (0.61 g, 3.3 mmol) in 10 mL of anhydrous THF was added to the flask. The reaction mixture was allowed to stir at -78 °C for 2 h. At this point, a solution of PIB-Br **47** (5.1 g, 2.1 mmol) in 20 mL of anhydrous THF was transferred to the flask by forced siphon. This solution was allowed to stir at -78 °C and slowly warmed to ambient temperature for 20 h. Then the reaction was quenched by adding 5 mL of methanol, and the solvent was removed under reduced pressure. The resulting residue was dissolved in 75 mL of hexane, and this phase was extracted 3 times with 20 mL of 90% ethanol/water and 3 times with 20 mL of brine. Then the hexane layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to obtain a crude product that was purified by silica gel column chromatography using hexane/ethyl acetate (9:1, v/v) as the eluent to obtain the product **49** (4.6 g, 74% yield) as light yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.58 (d, 2 H), 8.29 (s, 2 H), 7.19 (s, 2 H), 2.74 (m, 2.4 H), 2.48 (s, 2.4 H), 1.95-0.75 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 156.1, 153.2, 149.0, 148.9, 148.1, 124.6, 123.9, 122.0, 121.3, 59.5-22.7 (multiple peaks).

Synthesis of PIB-bound Ru(II)-bipyridine [Ru(PIB-bpy)$_3$Cl$_2$] complex (50). A 50-mL pressure vessel equipped with a magnetic stir bar was charged with PIB-bipyridine ligand **49** (1.53 g, 0.52 mmol), anhydrous $RuCl_3$ (31.2 mg, 0.15 mmol), 5 mL of heptane, and 5 mL of ethanol and sealed with a rubber septum. N_2 was bubbled through this solution for 15 min and then the rubber septum was replaced with the pressure vessel lid and closed tightly. This reaction mixture was allowed to stir at 90 °C for 24 h,

at which point the reaction mixture was cooled to ambient temperature and 5 mL of water was added. The mixture was transferred to a separatory funnel, and another 50 mL of hexane was added to the funnel. The top non-polar phase was separated and was extracted with 20 mL of 90% ethanol/water three times. Then the hexane layer was dried over anhydrous sodium sulfate, and the hexane solvent was removed under reduced pressure. This crude product was purified by chromatography using neutral alumina column as a support and dichloromethane/methanol (9:1, v/v) as the eluent to afford the desired product (1.39 g, 87% yield) as red viscous oil with a metal loading of 9.47×10^{-3} g of Ru/g of **50** as determined by ICP-MS. If **50** were formed without any fractionation of the PIB_{2300} phase tag, it should have had a molecular weight of 8914 Da. The 10,660 Da M_n for **50** calculated based on the ICP-MS analysis suggests that some fractionation of the PIB label occurred and that **50** is better described as having PIB_{2750} phase tags. The UV-visible spectroscopy of **50** had a λ_{max} = 465 nm in hexane that was comparable to the previously reported data for a similar $[Ru(PIB\text{-}bpy)_3Cl_2]$ complex in hexane that had a λ_{max} = 463 nm (ε = 15500 M^{-1} cm^{-1}).[82] ^1H NMR (300 MHz, $CDCl_3$) δ: 8.46 (m, 2 H), 7.66 (m, 2 H), 7.36 (m, 2 H), 2.84 (m, 2.6 H), 2.64 (s, 2.8 H), 1.95-0.75 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 156.5, 156.4, 156.3, 156.2, 154.7, 151.2, 151.0, 150.7, 150.6, 150.1, 150.0, 129.3, 129.2, 129.1, 129.0, 128.1, 127.9, 125.0, 124.1 84.7-14.1 (multiple peaks).

General procedure for oxidative C-C Bond cleavage catalyzed by 50. A 20-mL Schlenk tube equipped with a magnetic stir bar was charged with $[Ru(PIB\text{-}bpy)_3Cl_2]$ **50**

(178 mg, 16.6 μmol), 2,3-diphenylpropanal **51** (54 mg, 0.25 mmol), piperidine (75 μL, 0.75 mmol), 4.5 mL of dichloromethane, and 0.5 mL of acetonitrile. Then the Schlenk tube was connected to a balloon filled with oxygen, and the homogeneous reaction mixture was allowed to stir under the irradiation of a 30 W household fluorescent bulb at ambient temperature for 10 h. The reaction was followed by ^{1}H NMR spectroscopy. After the reaction was completed, the solvent was removed under reduced pressure. Hexane was added to dissolve the residue. This hexane phase was then extracted three times with 5-mL portions of acetonitrile. The catalyst containing hexane phase was recovered, the hexane was removed, and the recovered catalyst was reused for the following cycle with fresh substrate in 4.5 mL of dichloromethane and 0.5 mL of acetonitrile. The product containing acetonitrile was concentrated under reduced pressure to afford crude product. The crude product was then purified by silica gel column chromatography using hexane/ethyl acetate (19:1, v/v) as the eluenting solvent to yield the desired product **52** (51.6 mg/cycle, 96% yield) as light yellow waxy solid, mp = 48-53 °C (lit. 50-55 °C).[158]

1, 2-Diphenylethanone (52): ^{1}H NMR (300 MHz, CDCl3) δ (ppm): 8.07 (d, 2H), 7.60 (t, 1H), 7.50 (t, 2H), 7.36 (m, 5H), 4.34 (s, 2H); ^{13}C NMR (75 MHz, CDCl3) δ (ppm): 197.6, 136.6, 134.6, 133.2, 129.5, 128.7, 128.6, 126.9, 45.5.

General procedure for [2 + 2] cycloaddition of bis(enone) catalyzed by 50. A 20-mL Schlenk tube equipped with a magnetic stir bar was charged with [Ru(PIB-bpy)$_3$Cl$_2$] **50** (176 mg, 16.4 μmol), bis(enone) **53** (77.8 mg, 0.25 mmol), *N*,*N*-diisopropylethylamine

(100 μL, 0.57 mmol), and $LiBF_4$ (57.9 mg, 0.62 mmol). Addition of 4.5 mL of dichloromethane and 0.5 mL of acetonitrile formed a solution which was sealed with a rubber septum and degassed three times using the freeze pump thaw method. Then the reaction mixture was allowed to stir under the irradiation of a 30 W household fluorescent bulb at ambient temperature for 10 h. ^{1}H NMR spectroscopy was used to follow the reaction. After the reaction was complete, the solvent was removed under reduced pressure. At this point, hexane and acetonitrile were added to dissolve the residue. The two phases were separated and the hexane layer was extracted 3 times with 5 mL of acetonitrile. The catalyst containing hexane phase was isolated, the hexane was removed, and the recovered catalyst was reused for the following cycle with fresh substrate in 4.5 mL of dichloromethane and 0.5 mL of acetonitrile. The solvent was removed from the combined product-containing acetonitrile phases under reduced pressure to afford the crude products which were purified by silica gel column chromatography using hexane/ethyl acetate (19:1, v/v) as the eluent to yield the reductive cyclization product **54b** (30 mg/cycle, 39% yield), and hexane/ethyl acetate (9:1, v/v) as the eluent to yield the cycloaddition product **54a** (32.6 mg/cycle, 42% yield) as a white solid, mp = 148-153 °C (lit. 155-157 °C).[159]

(1*R*,5*S*,6*R*,7*S*)-6,7-Dibenzoylbicyclo[3.2.0]heptane (54a): ^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.78 (d, 4H), 7.47 (t, 2H) 7.38 (t, 4H), 3.89 (d, 2H), 3.23 (m, 2 H), 2.04 (m, 2H), 1.87 (m, 2H), 1.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 198.6, 136.3, 132.5, 128.5, 127.8, 48.3, 39.1, 32.5, 25.2.

2,2'-((1S,2S)-Cyclopentane-1,2-diyl)bis(1-phenylethanone) (54b): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.96 (dd, 4H), 7.56 (t, 2H), 7.47 (t, 4H), 3.22 (dd, 2H), 2.95 (dd, 2H), 2.20 (m, 2H), 1.99 (m, 2H), 1.64 (m, 2H), 1.29 (m, 2H); ^{13}C NMR (75 MHz, CDCl3) δ: 200.3, 137.2, 132.9, 128.6, 128.1, 44.0, 41.6, 32.5, 23.7.

Synthesis of PIB-bound iodide (83). A 250-mL round-bottomed flask equipped with a magnetic stir bar was charged with triphenylphosphine (3.64 g, 13.9 mmol), iodine (3.55 g, 28 mmol), imidazole (0.92 g, 13.5 mmol) and these reagents were dissolved in 100 mL of dichloromethane. After stirring for 10 min, a solution of PIB-bound alcohol **82** (14.7 g, 10.8 mmol) in 25 mL of dichloromethane was added dropwise to the reaction mixture. The reaction mixture was then allowed to stir at room temperature for 20 h. At this point, the solvent was removed under reduced pressure. The resulting residue was dissolved in 250 mL of hexane, and the hexane layer was extracted with 90% ethanol/water (50 mL × 2), DMF (25 mL × 3), and brine (50 mL). Then the hexane phase was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to afford the product **83** (16.1 g, 9.1 mmol, 84% yield) as colorless viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.28 (dd, 1 H), 3.14 (dd, 1 H), 2.05-0.85 (m).

Synthesis of PIB-bound triphenylphosphonium iodide (84). A 50-mL pressure vessel equipped with a magnetic stir bar was charged with PIB-bound iodide **83** (7.22 g, 4.1 mmol) and triphenylphosphine (4.0 g, 15.2 mmol) and 15 mL of toluene and 15 mL DMF were introduced. The vessel was sealed with a rubber septum and N_2 was bubbled

through the reaction mixture for 15 min. At this point, the rubber septum was replaced with the pressure vessel lid and closed tightly. The reaction mixture was allowed to stir at 160 °C for 48 h. Then the reaction mixture was allowed to cool to room temperature and diluted with 250 mL of hexane. The solution was transferred to a separatory funnel and was extracted with DMF (25 mL × 3), and brine (50 mL). Then the hexane layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by a neutral alumina column using dichloromethane/methanol (19:1, v/v) as the eluent to afford the desired product **84** (5.54 g, 3.6 mmol, 80% yield) as light yellow viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.81 (m, 16 H), 4.32 (m, 1 H), 3.17 (m, 1 H), 1.75-0.75 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 135.0, 133.8, 133.7, 132.1, 132.0, 131.9, 130.5, 130.4, 128.5, 128.4, 119.2, 118.6, 59.5-23.8 (multiple peaks).

Synthesis of PIB-bound bromobenzene (85). A 100-mL round-bottomed flask equipped with a magnetic stir bar was sealed with a rubber septum. Then a solution of PIB-bound triphenylphosphonium iodide **84** (5.33 g, 3.5 mmol) in 50 mL distilled anhydrous THF was transferred into the flask by forced siphon and cooled to -78 °C. Then 2.3 mL of a 1.6M solution of *n*-BuLi in hexane (3.68 mmol) was added to the flask by syringe, and the reaction mixture was allowed to stir at -78 °C. After stirring for 2 h, a solution of 4-bromobenzylaldehyde (0.9 g, 4.86 mmol) in 10 mL of THF was added to the flask via cannula. This reaction mixture was allowed to stir at -78 °C and slowly warmed to room temperature for 72 h. Then the reaction was quenched by methanol, and

the solvent was removed under reduced pressure. The resulting crude materials were dissolved in 200 mL of hexane and were extracted with 50 mL of 90% ethanol/water for three times. Then the hexane layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography using hexane as the eluent to afford the product **85** (3.64 g, 2.6 mmol, 74% yield) as colorless viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.48 (d, 2 H), 7.43 (d, 1 H), 7.22 (d, 1 H), 7.16 (d, 1H), 6.19 (m, 2H), 5.58 (dd, 1H), 2.89 (m), 2.53 (m), 1.95-0.75 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 142.5, 140.1, 137.0, 131.5, 131.3, 127.4, 125.9, 124.6, 120.2, 59.5-14.1 (multiple peaks).

Synthesis of PIB-bound bromobenzene (86). A 50-mL Schlenk flask equipped charged with a magnetic stir bar was charged with PIB-bound bromobenzene **85** (3.60 g, 2.57 mmol), 10 wt.% palladium on carbon (54.1 mg), 20 mL heptane and 20 mL ethyl acetate. Then this Schlenk tube was connected to a balloon filled with hydrogen, and the reaction mixture was allowed to stir for 48 h at room temperature. At this point, the reaction mixture was filtered through Celite, and the solvent was removed under reduced pressure to afford the product **86** (3.59 g, 2.54 mmol, 99% yield) as colorless viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40 (d, 2 H), 7.07 (d, 2 H), 2.57 (m), 1.65-0.85 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 142.0, 131.3, 130.1, 119.2, 59.5-14.1 (multiple peaks).

Synthesis of PIB-bound PTH (87). A 100-mL round bottom flask equipped with a magnetic stir bar was charged with PIB-bound bromobenzene **86** (3.46 g, 2.45 mmol),

phenothiazine (0.69 mg, 3.46 mmol), sodium *tert*-butoxide (0.46 g, 4.78 mmol), RuPhos (33.2 mg, 0.07 mmol), RuPhos precatalyst (62.5 mg, 0.08 mmol), and 50 mL of dioxane and was sealed with a rubber septum. The reaction mixture was allowed to stir at 110 °C for 20 h at which point the reaction was allowed to cool to room temperature. At this point, 150 mL of hexane was added, and the non-polar phase was extracted with water (30 mL), acetonitrile (30 mL × 3), and brine (30 mL). Then the hexane phase was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography using hexane as the eluent to obtain the product **87** (3.42 g, 1.96 mmol, 80% yield) as a light yellow viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42 (d, 2 H), 7.30 (d, 2 H), 7.01 (d, 2 H), 6.81 (m, 4 H), 6.20 (dd, 2 H), 2.71 (m), 1.95-0.85 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 144.5, 143.4, 138.2, 130.8, 130.7, 126.8, 126.6, 122.2, 119.7, 115.7, 59.5-11.4 (multiple peaks).

Procedure for polymerization of 89 catalyzed by 87 using DMA/heptane solvent mixture. A 20-mL vial equipped with a magnetic stir bar was charged with PIB-bound PTH **87** (26.5 mg, 15 μmol), methyl methacrylate (1 mL, 9.3 mmol) in 1.75 mL of heptane and 0.25 mL DMA and was sealed with a copper wired rubber septum. The mixture was degassed by freeze-pump-thaw for 3 cycles, and then ethyl 2-bromoisobutyrate (30 μL, 0.24 mmol) was injected via syringe. The reaction mixture was allowed to stir under the irradiation of a 23 W household fluorescent bulb at ambient temperature for 15 h. After the reaction, 1.5 mL of heptane was added to the vial

followed by adding 1.5 mL of DMA to insure that the catalyst and polymer were soluble in their respective phases. The mixture was centrifuged, and the DMA phase was removed. Then another 0.5 mL of DMA was added to extract any remaining polymer from the heptane phase. This DMA phase was separated from the heptane solution of **87** by centrifugation. The two DMA phases were combined and diluted with 2.5 mL of dichloromethane, and the polymer was precipitated by adding this solution to 100 mL of heptane. The polymer precipitate was isolated by vacuum filtration to afford the product **90** as a white solid (0.18 g/cycle). The catalyst containing heptane phase was concentrated under reduced pressure, and the recovered catalyst was reused for the following cycle by dissolving in 1.75 mL of heptane with 0.25 mL DMA, fresh monomer and initiator added. The product PMMA polymer **90** was characterized by NMR spectroscopy. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.61 (bs, -OCH_3), 1.83 (m, -CH_2-), 1.24 (m, isotactic methyl groups), 1.03 (bs, heterotactic methyl groups), 0.86 (bs, syndiotactic methyl groups); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 178.1, 177.8, 177.0, 54.4, 54.2, 51.8, 44.9, 44.5, 31.9, 22.7, 18.7, 16.5, 14.1. The PMMA product **90** was dissolved in THF and analyzed using a Viscotek gel permeation chromatograph that was calibrated with polystyrene standards to give the molecular weight (M_n) and molecular weight distribution (M_w/M_n) data of **90** shown in Table 5.

Procedure for polymerization of 91 catalyzed by 87 using a DMA/heptane solvent mixture. A 20-mL vial equipped with a magnetic stir bar was charged with PIB-bound PTH **87** (25.2 mg, 14.4 μmol), 2-ethoxyethyl methacrylate (1.6 mL, 9.8 mmol) in 2.1 mL

of heptane and 0.3 mL DMA. The mixture was degassed by freeze-pump-thaw for 3 cycles, and ethyl 2-bromoisobutyrate (30 μL, 0.24 mmol) were injected via syringe. The reaction mixture was allowed to stir under the irradiation of a 23 W compact fluorescent bulb at room temperature for 15 h. After the reaction, 2 mL of heptane was added to the vial followed by adding 2 mL of DMA to dissolve the polymer. The mixture was centrifuged, and the DMA phase was removed. Then another 1 mL of DMA was added to extract the polymer and removed after centrifugation. The DMA phases were combined and diluted with 2.5 mL of dichloromethane, and the precipitation was achieved by adding 70 mL of heptane. The supernatant was removed and the polymer precipitates were dried under vacuum to afford the product **92** as a waxy gel (1.01 g/cycle). The catalyst containing heptane phase was concentrated under reduced pressure, and the recovered catalyst was reused for the following cycle by dissolving it in 2.1 mL of heptane with 0.3 mL DMA, fresh monomer and initiator added. The product polymer **92** was characterized by NMR spectroscopy and GPC. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.09 (bs, -OCH_2-), 3.62 (bs, -OCH_2-), 3.52 (bs, -OCH_2-), 2.14-1.84 (m, -CH_2-), 1.22 (bs, -$CH_2\underline{CH_3}$), 1.07 and 0.92 (bs, stereoisomeric methyl groups); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 177.7, 177.3, 176.6, 67.9, 67.7, 66.5, 64.0, 54.2, 45.1, 44.7, 15.2. The PEEMA product **92** was dissolved in THF and analyzed using a Viscotek gel permeation chromatograph that was calibrated with polystyrene standards to give the molecular weight (M_n) and molecular weight distribution (M_w/M_n) data of **92** shown in Table 5.

Kinetic study of light-mediated polymerization catalyzed by 87. A 20 mL vial equipped with a magnetic stir bar was charged with benzyl methacrylate (1.7 mL, 10 mmol), PIB-bound PTH **87** (26.1 mg, 15 μmol), and 2 mL of THF and sealed with a copper wired rubber septum. The reaction mixture was degassed by freeze-pump-thaw for 3 cycles, and ethyl α-bromophenylacetate (35 μL, 0.2 mmol) were injected via syringe. The reaction mixture was allowed to stir under the irradiation of a 23 W compact fluorescent bulb at room temperature. Aliquots of the reaction mixture were removed from the vial by syringe at different time points and were analyzed by ^{1}H NMR spectroscopy to determine the conversions of the monomer. The PBnMA product **95** was dissolved in THF and analyzed using a Viscotek gel permeation chromatograph that was calibrated with polystyrene standards to give the molecular weight (M_n) and molecular weight distribution (M_w/M_n) data of **95** at different conversions that are shown in Figure 22. The PBnMA product **95** was also characterized by NMR spectroscopy. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.28 (bs, phenyl), 4.90 (bs, -OCH_2-), 1.96 (m, -CH_2-), 0.94 and 0.75 (bs, stereoisomeric methyl groups); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 177.4, 177.1, 176.4, 136.4, 135.1, 128.5, 128.4, 128.2, 66.8, 45.1, 44.7.

^{1}H NMR spectroscopic analysis for contamination of 87 in PMMA, PEEMA, and PBnMA polymer products. PIB_{1000} has a broad singlet at 1.14 δ for the 102 protons of the 34 methyl groups of the repeating subunits in this polymer. Figure 28 shows the same ^{1}H NMR spectral region of PMMA. There is a miniscule peak at 1.14 δ whose area integration is 1 which represent 102 protons per mole of PIB. There are peaks at 1.03

and 0.87 δ for the methyl groups of PMMA.[131,132] These peaks have a total integral of 224. The M_n value for this PMMA product was 3300 Da. Thus, the degree of polymerization is 33 and these signals with an integral of 224 correspond to 99 protons per mole of PMMA. The relative area of the signals due to the moles of PMMA and the moles of PIB is 2.26/0.01, and the calculated mol% of PIB present in this PMMA product is 0.44 mol% which corresponds to 0.17 wt% of PIB in the PMMA product. A similar calculation for the PEEMA product and the PBnMA product shows that PIB contamination in those products was 0.48 wt% and 0.11 wt% respectively.

Synthesis of PIB-bound carboxylic acid (113). A 100-mL round-bottomed flask equipped with a magnetic stir bar was charged with *tert*-butyl isobutyrate (0.82 g, 5.7 mmol) and 40 mL of distilled anhydrous THF and sealed with a rubber septum. The flask was cooled to -78 °C, and then LDA (2.3 mL, 4.6 mmol) was added by syringe. The reaction mixture was allowed to stir at -78 °C for 2 h. At this point, a solution of PIB-bound iodide (4.84 g, 2.0 mmol) in 20 mL of anhydrous THF was transferred to the flask by forced siphon. This reaction mixture was allowed to stir at -78 °C and slowly warmed to ambient temperature for 24 h. Then the solvent was removed under reduced pressure. The resulting material was dissolved in 200 mL of hexane and was extracted with acetonitrile (35 mL × 3) and brine (50 mL). The hexane layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to afford the crude PIB-bound *tert*-butyl ester **112** (4.6 g) that was used directly in the next step without further purification. A 50-mL round-bottomed flask equipped with a magnetic

stir bar was charged with the ester **112** (4.6 g), H_2SO_4 (0.28 g, 2.8 mmol), and 50 mL of dichloromethane. The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The resulting material was dissolved in hexane with a few drops of triethylamine added and was extracted with brine. The hexane layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography using hexane/ethyl acetate (17:3, v/v) as the eluent to afford the PIB-bound carboxylic acid **113** (3.22 g, 59% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.70-0.86 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 184.9, 60.2-29.8 (multiple peaks). IR (cm^{-1}): 2951, 2895, 1699, 1470, 1389, 1366, 1229, 949, 922.

Synthesis of PIB-bound Rh complex (114). A 100-mL round-bottomed flask equipped with a stir bar was charged with PIB-bound carboxylic acid **113** (3.08 g, 1.1 mmol), rhodium acetate (0.14 g, 0.32 mmol), and 50 mL of toluene. The reaction mixture was refluxed under nitrogen for 24 h. Then the reaction mixture was allowed to cool to room temperature, and the solvent was removed under reduced pressure. The material obtained was dissolved in 200 mL of hexane and was extracted with 90% ethanol/water for 3 times. The hexane layer was dried over anhydrous sodium sulfate, and solvent was removed under reduced pressure to afford the PIB-bound Rh complex **114** as a dark green viscous oil (3.2 g, 57% yield) with a Rh loading of 0.098 mmol/g that was determined based on ICP-MS analysis.

General procedure for cyclopropanation of styrene in continuous-flow system. A separatory cylinder was charged with 25 mL of acetonitrile, and then a solution of catalyst **114** (0.43 g, 0.02 mmol) in 15 mL of heptane was added. The catalyst-containing heptane phase was pumped into the continuous-flow system using a Viscotek HPLC pump at a flow rate of 1.5 mL/min. Ethyl diazoacetate (0.63 g, 5.25 mmol) and styrene (10.5 g, 0.1 mol) was loaded in a gastight syringe. The flow rate of the HPLC pump was adjusted to 0.05 mL/min when the catalyst-containing heptane solution kept circulating in the system. Then the mixture of ethyl diazoacetate and styrene were pumped into the flow system using a syringe pump at a flow rate of 0.4 mL/h. The two streams were mixed at a T-shape connector and passed through a 1.6 meter-long PFA tubing with 1/8" OD and 1/16" ID. The outlet of the tubing was immersed into the bottom acetonitrile phase in the separatory cylinder. The flow reaction was carried out at room temperature for 31 h. After the reaction, the acetonitrile phase was collected, and the solvent was removed under reduced pressure to give the crude product that was purified by silica gel column chromatography using hexane/ethyl acetate (10:1, v/v) as the eluent to afford the final product (0.68 g, 68% yield). The NMR data of the product agreed with our previously reported data.[152]

General procedure for RCM of diene in continuous-flow system. A separatory cylinder was charged with 25 mL of acetonitrile, and then a solution of catalyst **115** (0.33 g, 0.06 mmol) in 15 mL of heptane was added. The catalyst-containing heptane phase was pumped into the continuous-flow system using a Viscotek HPLC pump at a

flow rate of 1.5 mL/min. A solution of diethyl diallylmalonate (1.21 g, 5 mmol) in 4 mL of heptane was loaded in a gastight syringe. The flow rate of the HPLC pump was adjusted to 0.05 mL/min when the catalyst-containing heptane solution kept circulating in the system. Then the mixture of ethyl diazoacetate and styrene was pumped into the flow system with a syringe pump at a flow rate of 0.3 mL/h. The two streams were mixed at a T-shape connector and passed through a 1.6 meter-long PFA tubing with 1/8" OD and 1/16" ID. The outlet of the tubing was immersed into the bottom acetonitrile phase in the separatory cylinder. The flow reaction was carried out at room temperature for 18.3 h. After the reaction, the acetonitrile phase was collected, and the solvent was removed under reduced pressure to afford the crude product (1.04 g, 73% yield).

CHAPTER VII

CONCLUSIONS

In conclusion, our group interests in the development of more environmentally benign chemical processes, especially utilizing soluble polymer support for recovery and reuse of homogeneous catalysts. The work described in this dissertation shows new roles of PIB as a nonpolar soluble polymer support in the development of green synthetic strategies. A recyclable PIB-bound Rh(II) carboxylate complex was prepared and used to carry out cyclopropanation and O-H insertion reactions in a heptane/acetonitrile biphasic solvent mixture. The results show that the enforced phase-selective solubility of the PIB-bound Rh(II) catalyst can be used not only to recycle the catalyst but also to suppress the undesired dimerization reaction without using slow syringe pump addition of the ethyl diazoacetate. This suppression of by-product formation is shown to be due to the increased phase segregation of the PIB-bound catalyst and the diazo substrate. These studies also suggest that added unfunctionalized hydrocarbon polymer cosolvents can function as antileaching agents, decreasing the leaching of a soluble polymer-bound species into the polar phase in a biphasic solvent mixture.

The applications of PIB as a soluble polymer support in recycling of the photoredox catalysts are also demonstrated. A PIB-bound Ru(II)-bipyridine complex was prepared, and we show that this PIB-supported Ru(II) complex can be used as a recyclable catalyst to carry out visible light-mediated oxidative C-C bond cleavage of aldehyde in CH_2Cl_2/CH_3CN homogeneous system. In addition, [2 + 2] cycloaddition of

bis(enone) can also occur with high conversions using this PIB-supported Ru catalyst. The results indicated that this PIB-supported Ru catalyst can be successfully recycled and reused for at least 5 cycles with no loss of catalytic activity and with leaching levels of ca. 1% of the charged catalyst. However, these studies indicate a limitation of using this PIB-supported catalyst in reactions that require a more polar solvent medium based on the evidence of longer reaction times, varying selectivity, or no reaction occurring.

We further explored the strategy of using PIB in recycling of the organic photoredox catalyst and developed a method to separate and recycle the catalyst in polymer synthesis. The preparation of a PIB-bound 10-phenylphenothiazine (PIB-PTH) catalyst was described. This PIB-supported catalyst can be used as a recyclable photoredox catalyst to conduct the visible light-mediated radical polymerizations of various methacrylate monomers in THF or a heptane/DMA solvent mixture. The results show that this PIB-bound organocatalyst can successfully effect the polymerizations and afford modest control over the molecular weight and the polydispersity of the polymer products. In addition, the polymerization occurs when exposed to light and stops in the dark that is similar to the low molecular weight PTH catalyst.

We also designed a continuous-flow reaction system to carry out homogeneous catalytic reactions using PIB-bound transition-metal catalysts. The results of a PIB-bound Rh complex catalyzed styrene cyclopropanation reaction in the flow system are comparable to the previously reported results under batch conditions, and the desired products formed in satisfactory yield with modest dimerization of ethyl diazoacetate occurred. The PIB-bound Hoveyda-Grubbs second generation catalyst catalyzed RCM

of diethyl diallylmalonate was also performed under flow conditions. These results show that the PIB-supported catalysts can be continuously reused under flow conditions.

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